2ª Parte

Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

- PCT ENTRADA EN FASE NACIONAL -

21. **EXPEDIENTE No.** 06111125

54. **TÍTULO** DERIVADOS DE TETRAHIDROQUINOLINA Y UN PROCEDIMIENTO PARA PREPARAR LOS MISMOS

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** TANABE SEIYAKU CO., LTD.

DOMICILIO 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505 - JAPON

74. **APODERADO** DRA. MARGARITA CASTELLANOS ABONDANO

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-111125- -00000-0000
Fec: 2006-11-01 14:40:30 Dep: 2020 NUEVAS SOLICITUDES
Tra: 11 PATENTES Y NUEVAS VARIEDADES
Eve: 379 FASE NACIONAL II
Act 411 PRESENTACION Folios: 884

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

02/11/06

SOLICITUD DE:

①

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

[ ] Capítulo I [X] Capítulo II

② **SOLICITANTE (71)**	Nombre TANABE SEIYAKU CO., LTD. Dirección 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505, JAPON Nacionalidad o Domicilio Osaka, JAPON Lugar de Constitución JAPON Teléfono Fax E-mail	IDENTIFICACIÓN C C [ ] NIT [ ] C E [ ] Otro [ ] Cual Número
③ **REPRESENTANTE O APODERADO (74)**	Nombre MARGARITA CASTELLANOS A. Dirección. CALLE 94A No. 7A-09 Teléfono 610 7420 Fax 610 0706 E-mail info@castellanosyco.com	IDENTIFICACIÓN C C [X] NIT [ ] C E [ ] Otro [ ] Cual Número 39'779.654 TPA 70 819
④ **INVENTOR (ES) (72)**	Nombre HITOSHI KUBOTA, MASAKATSU SUGAHARA, MARIKO FURUKAWA, MAYUMI TAKANO y DAISUKE SUDO Dirección VER ANEXO # 1 Nacionalidad o Domicilio JAPONESES	

⑤ **PCT (86)**

Solicitud Internacional No PCT/JP2005/006894 Fecha 01/04/2005

Publicación Internacional No WO 2006/095409 A2 Fecha 13/10/2005

⑥ **Título (54)** DERIVADOS DE TETRAHIDROQUINOLINA Y UN PROCEDIMIENTO PARA PREPARAR LOS MISMOS

⑦ **Clasificación Internacional (51)** C07D 491/04, 401/14, 401/04, A61K 31/47, 31/4545, 31/444, 31/4439, A61P 3/06

⑧ **Prioridad** SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	02/04/2004	2004-109550

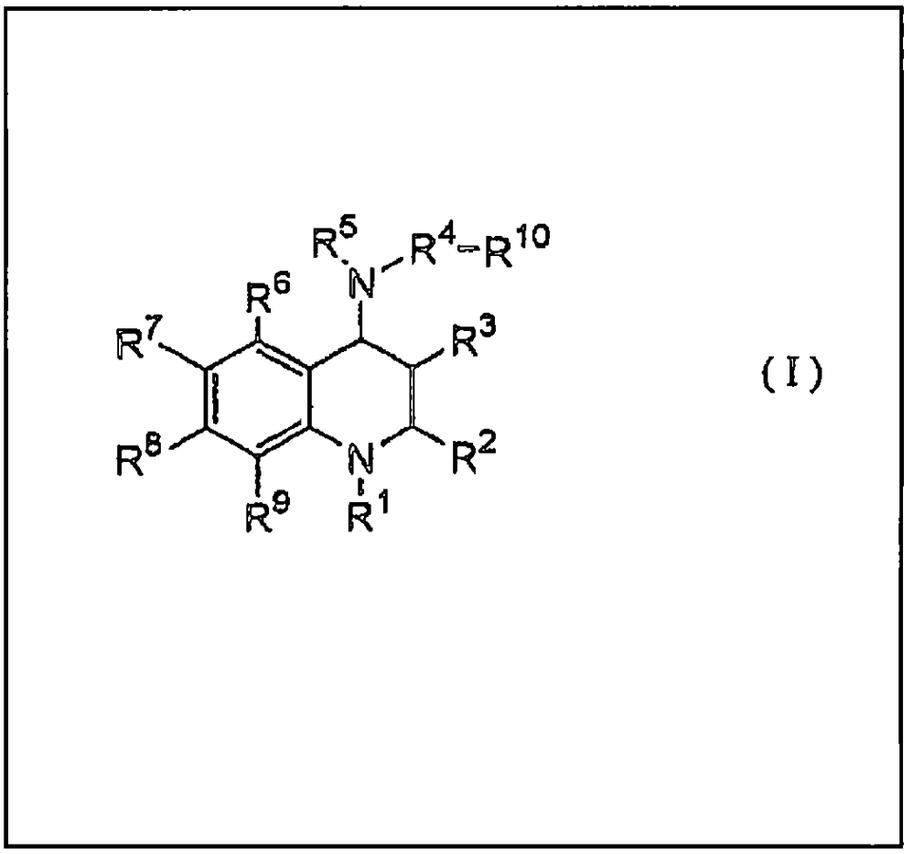
⑨ **Comprobante de pago No.** 06-77,357 **Fecha** Octubre 6 de 2006

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

(10) **Anexos**

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [X] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indigenas.
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o titulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros **Tarjeta Propietario, Tarjeta Temática, Extracto para la Publicación, disquet con el extracto para la publicación y formato PCT/IB/306, donde se confirma un cambio de dirección.**

(11) **FIGURA CARACTERISTICA:**



(I)

(12) **Solicito la concesión de la patente,**

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA.

C.C. No. 39'779.654 Usaquén - TPA 70.819 C.S.J.

JUN. 2006

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - 6079-FNPCT

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

ANEXO # 1

INVENTOR(ES) (72)

	NOMBRE	DIRECCION	NACIONALIDAD O DOMICILIO
1	**HITOSHI KUBOTA**	c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505, JAPON	JAPONES
2	**MASAKATSU SUGAHARA**	c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505, JAPON	JAPONES
3	**MARIKO FURUKAWA**	c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505, JAPON	JAPONES
4	**MAYUMI TAKANO**	c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505, JAPON	JAPONES
5	**DAISUKE SUDO**	504, Domiru-Sagamiono, 3-1, Sagamiono 8-chome, Sagamihara-shi, Kanagawa 228-0803, JAPON	JAPONES

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

6079
4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-111125- -00000-0000
Fec: 2008-11-01 14:30:30 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act 411 PRESENTACION Folios: 884

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 77,357
FECHA : OCTUBRE 6 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO POPULAR	050-00110-6	53373599	06/10/2006	1,516,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000 00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE . _____

CASTELLANOS & CO LTDA
A B O G A D O S
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E S. D

Ref. **PODER** conferido por **TANABE SEIYAKU CO., LTD.**

Yo, **XIMENA CASTELLANOS ABONDANO,** mayor de edad, identificada y domiciliada como aparece al pié de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra. **MARGARITA CASTELLANOS ABONDANO,** el poder que me confirió **TANABE SEIYAKU CO., LTD.**, con domicilio en **2-10 Dosho-machi 3-chome, Chuo-ku, Osaka, JAPON**, debidamente legalizado por el Ministerio de Relaciones Exteriores bajo el No **027082** el día **15 de Abril de 1997**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de patente PCT Entrada en Fase Nacional en Colombia, para: **"DERIVADOS DE TETRAHIDROQUINOLINA Y UN PROCEDIMIENTO PARA PREPARAR LOS MISMOS".-**

Del Señor Jefe,

Acepto

Ximena Castellanos Abondano
C.C No **39.773.330** de Usaquén
T P A. No. **58.236** del C.S.J
Calle 94 A No. 7 A-09 – Bogotá
PBX· 610 74 20

Margarita Castellanos Abondano
C.C. No **39.779.654** de Usaquén
T P.A. No **70.819** del C.S J
Calle 94 A No. 7 A-09 – Bogotá
PBX· 610 74 20

Bogotá, D C.
XCA/MCA/gcb/6079-FNPCT

(Art. 84 C.P.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Ante su Notario Cuarenta y Uno (41) del circulo
de esta ciudad comparecio personalmente
Ximena Castellanos
identificado con C.C 39.79.330
expedida en Usaq y tarjeta profesio-
nal de abogado(a) No 58236 del Consejo
Superior de la Judicatura, con documento di-
rigido a Superintendencia
y la firma puesta en este escrito es
suya. de Industria

Firma del declarante

En Bogota D.C. 25 OCT. 2006

AUTORIZO ESTA DILIGENCIA EL SUSCRITO NOTARIO

Carrera 12 N° 93-26
AGUSTIN GORALES RIVERA

(Art. 84 C.P.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Ante su Notario Cuarenta y Uno (41) del circulo
de esta ciudad comparecio personalmente
Margarita Castellanos
identificado con C.C 39.796.54
expedida en: Usaq, y tarjeta profesio-
nal de abogado(a) No 70819 del Consejo
Superior de la Judicatura, con documento di-
rigido a Superintendencia
y la firma puesta en este escrito es
suya.

Firma del declarante

En Bogota D.C. 25 OCT. 2006

AUTORIZO ESTA DILIGENCIA EL SUSCRITO NOTARIO

REPUBLICA DE COLOMBIA
Circulo de Santafe
de Bogota D.C.
OFC AU

Carrera 12 N° 93-26
AGUSTIN GORALES RIVERA

4561

6

PODER

El(los) suscrito(s) en representación de TANABE SEIYAKU CO., LTD.

domiciliado(s) en 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka, JAPON

nombra por el presente a Ximena Castellanos A. y/o Margarita Castellanos A. abogados, con oficinas en 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; depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de su traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencia de uso de esos derechos; b) acciones de oposición, 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 este mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Dado y firmado hoy 11 de Marzo de 1997

en Osaka, Japón

POWER OF ATTORNEY

I (we) the undersigned

TANABE SEIYAKU CO., LTD.

of 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka, Japan

hereby grant(s) Power of Attorney to Ximena Castellanos A. y/o 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 wich purpose we authorize the said attorneys to represent us before any authorities or persons, specially those administrative, administrative contentious and judicial, in all matters concerning the following: a) Obtainment of patents, models and designs; the registration of trademarks, service, collective and defensive marks; the deposit of commercial names and ensigns; its renewal, extensión, recordal of assignments, change of name or domicile, voluntary cancellation; and the registration of licences of use of the above rights; b) Actions of opposition cancellation, nullity, infringement, granting of licences; and in general the civil, penal an administrative suits relating to those rights; 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- infact in or out of Court

Given and signed this 11th day of March, 1997

in Osaka, Japan

TANABE SEIYAKU CO., LTD.

By: Ichiro Chibata

Ichiro Chibata, Ph. D.
President and Chief Executive Officer,
Representative Director

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

OSAKA LEGAL AFFAIRS BUREAU
NOTARY
1-3, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPAN

Esta copia concuerda con el original que tuve a la vista
Bogotá D.C.
25 OCT 2006

公証人

印

印

登簿平成9年第208号

当公証人は次の認証をする。

田辺製薬株式会社　代表取締役　千畑一郎

上記の者は代理人　稲本暢子により当公証人の面前でこの証書の署名を自認した。

上記の会社は日本国大阪府大阪市中央区道修町3丁目2番10号に所在し日本の法律に基いて設立された会社であり千畑一郎は同会社の代表取締役であることを大阪法務局発行の証明書によつて相違ないことが認められるものである。

平成9年3月19日於本職役場

大阪市中央区平野町2丁目1番2号(沢の鶴ビル内)

大阪法務局所属

公証人　山田敬二郎

Esta copia coincide con el original que tuvo a la vista
Bogotá, D.C.
25 OCT 2006

8

REGISTERED NUMBER: 208/1997

This is to certify that Ms. Nobuko INAMOTO, an agent of Dr. Ichiro CHIBATA, has stated in my very presence that said Dr. Ichiro CHIBATA acknowledges himself to have signed to the attached Power of Attorney as the Representative Director of TANABE SEIYAKU CO., LTD. having a place of business at 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka, Japan, a corporation organized and existing under the laws of Japan; and that said Dr. Ichiro CHIBATA has signed this instrument in compliance with the authority bestowed on him within the objects set forth in the articles of incorporation and by the laws of the said corporation.

I further certify that I have convinced myself by inspection of the certified copy of the commercial extract of TANABE SEIYAKU CO., LTD., issued by the Osaka Legal Affairs Bureau, Japanese Government, dated February 7, 1997 that said Dr. Ichiro CHIBATA's signature is binding on the said corporation.

At the Office of Keijiro YAMADA, Osaka, Japan
On the 19th day of March, 1997.

Keijiro Yamada

Keijiro YAMADA
Notary attached to The
Osaka Legal Affairs
Bureau

c/o Sawanotsuru Building
No. 1-2, 2-chome, Hirano-machi,
Chuo-ku, Osaka-shi, Osaka-fu,
Japan

OSAKA LEGAL AFFAIRS BUREAU
NOTARY
1-2, HIRANO-MACHI, 2 CHOME
CHUO-KU, OSAKA JAPAN

25 OCT 2006

総第 600 号

証　明

大阪法務局所属公証人　山田敬二郎

平成 9 年 3 月 17 日付

平成 9 年第 208 号

この認証の付与は、右嘱申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。

但し、公証人の欧文証明は省略する。

平成 9年3月24日

平成　　年　　月　　日

大阪法務局長　下村治藏

No. 1648

For legalization by the foreign consul in Japan, this is to certify that the Seal affixed hereto is genuine.

Osaka, MAR. 24. 1997

Official

Ministry of Foreign Affairs
(Consular and Migration Policy Division)

Esta copia coincide con el original que tuve a la vista

25 OCT 2006

CONSULADO GENERAL DE COLOMBIA

TOKIO-JAPON

El suscrito, Encargado de las Funciones Consulares en Tokio, vistos los siguientes documentos:

1) Certificado de registro mercantil de la compañía;
2) Certificado auténtico sobre autorización para otorgar el poder;

C E R T I F I C A :

Que la compañía TANABE SEIYAKU CO., LTD.
es una sociedad constituida de acuerdo con las leyes del Japón y cumple su objeto social conforme a las mismas.
Que el señor ICHIRO CHIBATA en su carácter de REPRESENTATIVE DIRECTOR
de la citada compañía, está autorizado para conferir el poder adjunto.
Que el señor KUNITERU NISHIBERI , quien autentica el mencionado documento, es funcionario autorizado de la División Consular del Ministerio de Relaciones Exteriores del Japón, y su firma coincide con la registrada en este Consulado.
El Encargado de las Funciones Consulares no asume responsabilidad alguna por el contenido del documento adjunto.

Tokio, 31 de marzo de 1.997

CONSULADO GENERAL DE COLOMBIA TOKIO

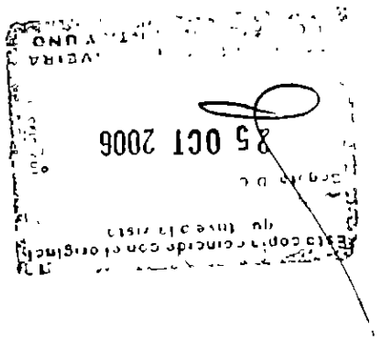
Luis A. Hernández S.
Segundo Secretario
Encargado de
las Funciones Consulares

Número: 43

Derechos: US$106 (Resolución 2570, Sep.30/92)
(Ciento seis dólares)

PAGADO IMPUESTO DE TIMBRE

Esta copia coincide con el original que tuve a la vista
25 OCT 2006



MINISTERIO DE RELACIONES
EXTERIORES

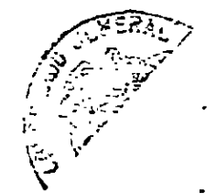
021082

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

97 APR 15 PM 12:01

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.



----------TRADUCCION OFICIAL No. 97-04-21----------

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora Oficial No. 2755/68 de Minjusticia, al igual que la presente.-

(Anexos a un poder otorgado por TANABE SEIYAKU CO. LTD.)

Registro No. 208/1997

La presente es para certificar que Nobuko Inamoto, agente de Ichiro CCHIBATA ha manifestado en mi propia presencia que dicho Dr. Ichiro CHIBATA reconoce el mismo haber firmado el poder adjunto como el Director Rpresentante de TANABE SEIYAKU CO., LTD., con domicilio social en 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka, Japón, una sociedad organizada y existente bajo las leyes del Japón; y que dicho Dr. Ichiro CHIBATA ha firmado este instrumento en cumplimiento con la autoridad conferida a él dentro de los objetos establecidos en los artículos de constitución y de los estatutos de dicha sociedad.

Certifico además que me percatado yo mismo por inspección de la copia certificada ddel extracto comercial de TANABE SEIYAKU CO., LTD. expedido por la Oficina de Asuntos Legales de Osaka, Gobierno Japonés, de fecha Febrero 7, 1997 que la [illegible] de dicho Dr. Ichiro CHIBATA obliga a dicha sociedad.

En la oficina de Keijiro YAMADA, Osaka, Japón, el día 11 de Marzo de 1997.

(fdo) Keijiro Yamada

Keijiro YAMADA

Notario adjunto a la Oficina de

Asuntos Legales de Osaka

Esta copia coincide con el original que tuve a la vista

25 OCT 2006

c/o Sawanotsuru Building

No. 1-2, 2-chome, Hirano-machi

Chuo-ku, Osaka-shi, Osaka-fu

Japón

(Sello) Oficina de Asuntos Legales de Osaka

NOTARIO

1-2, Hirano-machi, 2-chome,

Chuo-ki, Osaka, Japón

No. 1648

Para legalización por el consul extranjero en Japón. La presente es para certificar que el sello fijado al presente es auténtico.

Osaka, Marzo 24, 1997

(fdo) ilegible

Funcionario

Ministerio de Relaciones Exteriores

(Segunda División Consular y de Policia de Emigración)

(Sellos)

EN ESPAÑOL, La certificación sobre la existencia de la sociedad y el cargo de su Director Representante y legalización de la firma de K. Nishiberi por el Consulado de Colombia en Tokyo, Japón, el 31 de Marzo de 1997, No. 43 y autenticación de la firma consular por el Ministerio de Relaciones Exteriores.

Es fiel copia del original que tuvo a la vista

Bogotá D.C.

25 OCT 2006

FIRMA
UNO

Colombia bajo el numero 027082 de Abril 15, 1997.

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, Abril 18, 1997

MARIA [illegible] DUQUE T.
INTERPRETE OFICIAL
[illegible] MINJUSTICIA

NO SE ASUME RESPONSABILIDAD DEL TEXTO
97 APR 25 [illegible]08
JEFE DE LEGALIZACIONES
SUPERVISOR ENCARGADO

MINISTERIO DE RELACIONES EXTERIORES
030127
FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA FUNCIONES INDICADAS

Esta copia coincide con el original que tuve a la vista
Bogotá D.C.
25 OCT 2006

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2005 (13.10.2005)

PCT

(10) International Publication Number
WO 2005/095409 A2

(51) International Patent Classification[7]: C07D 491/04, 401/14, 401/04, A61K 31/47, 31/4545, 31/444, 31/4439, A61P 3/06

(21) International Application Number: PCT/JP2005/006894

(22) International Filing Date: 1 April 2005 (01.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2004-109550 2 April 2004 (02.04.2004) JP

(71) Applicant *(for all designated States except US)*: **TANABE SEIYAKU CO., LTD.** [JP/JP], 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUBOTA, Hitoshi** [JP/JP]; c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP). **SUGAHARA, Masakatsu** [JP/JP], c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP). **FURUKAWA, Mariko** [JP/JP]; c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP). **TAKANO, Mayumi** [JP/JP]; c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP). **MOTOMURA, Daisuke** [JP/JP], c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP).

(74) Agents: **KAWAMIYA, Osamu** et al., AOYAMA & PARTNERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 5400001 (JP).

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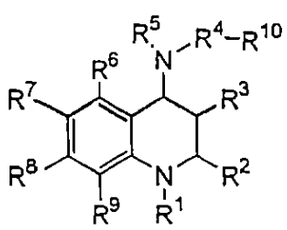
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(54) Title: TETRAHYDROQUINOLINE DERIVATIVES AND A PROCESS FOR PREPARING THE SAME



(I)

(57) Abstract: A novel compound of the formula (I) wherein R^1 is alkoxycarbonyl or the like, R^2 is alkyl or the like; R^3 is hydrogen or the like; R^4 is alkylene or the like, R^5 is optionally substituted heterocyclic group; R^6, R^7, R^8 and R^9 are independently hydrogen, alkyl, alkoxy, or the like; R^{10} is optionally substituted aromatic ring, or the like; or a pharmaceutically acceptable salt thereof, which has an inhibitory activity against cholesteryl ester transfer protein (CETP).

DESCRIPTION

TETRAHYDROQUINOLINE DERIVATIVES AND A PROCESS FOR PREPARING THE SAME

TECHNICAL FIELD

The present invention relates to a novel tetrahydroquinoline derivative having an inhibitory activity against cholesteryl ester transfer protein (CETP).

BACKGROUND ART

Hypercholesterolemia, especially high serum level of low-density lipoprotein (LDL) cholesterol, has been revealed to be a risk factor of arteriosclerotic diseases by a number of epidemiological surveys. Actually, drugs capable of decreasing LDL cholesterol level such as 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors have been used with the aim of preventing coronary artery diseases, and demonstrated to have some benefits in many large scale clinical tests. However, their preventive effect on coronary diseases is limited to some extent, and is not satisfactory enough yet.

Recently, low serum level of high density lipoprotein (HDL) cholesterol has been revealed to be a potent risk factor of arteriosclerotic diseases by a number of epidemiological surveys and large scale clinical tests. HDL is known to have various antiarteriosclerotic effects and attnetion is focused on the potentiality of drugs increasing HDL cholesterol level as a means for prevention or treatment of arteriosclerotic diseases. However, there are no drugs that can be used in a satisfactory manner for this purpose. Fibrates and HMG-CoA reductase inhibitors have only low activity of increasing HDL cholesterol; nicotinic acid derivatives can significantly increase HDL, but have serious toleration issues. Accordingly,

there has been a demand for a well-tolerated agent which can significantly elevate HDL cholesterol levels, thereby preventing or reversing the progression of atherosclerosis.

It is known that many proteins are involved in the regulation mechanism for catabolism of various lipoproteins. Among them, the role of cholesteryl ester transfer protein (CETP) became to draw attention. CETP is a protein responsible for transfer of cholesteryl ester (CE) and triglyceride between lipoproteins, and mediate the transfer of CE from HDL to LDL or to very low density lipoprotein (VLDL). Accordingly, CETP activity affects greatly the lipid composition in lipoprotein particles. For example, it is known that administration of a neutralizing monoclonal antibody to CETP to rabbit or hamster elevates HDL cholesterol levels and lower LDL cholesterol levels. Furthermore, human being having decreased or eliminated CETP activity due to gene mutation shows raised blood HDL cholesterol level and lowered blood LDL cholesterol level. On the other hand, it is known that transgenic mice and rats made to express CETP show lowered HDL cholesterol level and raised LDL cholesterol level. Thus, it is considered that CETP greatly contribute to the regulation of serum lipids, and thereby affecting the change of serum lipid profile such as decrease of HDL cholesterol level and increase of LDL cholesterol. Accordingly, it is assumed that a high value of CETP activity would induce arteriosclerosis.

In fact, CETP activity varies depending on animal species. It is known that, arteriosclerotic lesions are readily formed by cholesterol loading in animals with high CETP activity such as rabbits, whereas such lesions hardly occur in animals with low CETP activity such as rats. Furthermore, it is confirmed that continuous suppression of CETP activity by administration of antisense oligodeoxynuclotide resulted in effects such as increase of blood HDL cholesterol level and reduction in arteriosclerotic lesions in cholesterol-fed rabbits.

The above findings indicate that CETP activity is in negative correlation with HDL cholesterol, and that inhibition of CETP activity would decrease the degree of risk for arteriosclerotic diseases. It is therefore expected that compounds capable of inhibiting CETP activity can block the transfer of cholesterol from HDL to LDL, and thereby increasing HDL cholesterol that tends to prevent arteriosclerosis while lowering LDL cholesterol that tends to promote arteriosclerosis. In this way, such compounds can serve as a useful preventive or therapeutic agent for arteriosclerotic diseases, hyperlipemia or dyslipidemia and provide effective medical treatment for the first time.

Examples of compounds having CETP inhibitory activity include tetrahydroquinoline derivatives. See, WO00/17164, WO00/17165, WO00/17166.

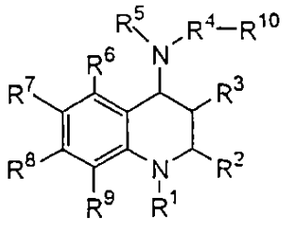
However, these compounds have defects That is, they are poorly soluble in water and cannot be absorbed enough in vivo, a sufficient blood level for taking medicinal effect can hardly be achieved even when administered as an ordinary formulation for oral administration. See, WO03/63868.

Accordingly, novel compounds in which the above-mentioned defects have been solved are highly demanded.

DISCLOSURE OF INVENTION

The present invention provides novel tetrahydroquinoline derivatives having an excellent CETP inhibitory activity wherein defects of existing CETP inhibitory compounds are rectified.

Thus, the present invention provides a compound of the formula (I):



(I)

wherein R^1 is a hydrogen atom, an optionally substituted alkoxycarbonyl group, an optionally substituted carbamoyl group, an optionally substituted alkyl group, an optionally substituted alkanoyl group, a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), or a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted),;

R^2 is a hydrogen atom or an optionally substituted alkyl group;

R^3 is a hydrogen atom or an optionally substituted alkyl group;

R^4 is an optionally substituted alkylene group;

R^5 is a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen sulfur and nitrogen atoms, wherein the heterocyclic group is substituted by 1 to 5 substituents selected from the following groups, or said heterocyclic group is substituted by 1 to 5 substituents selected from the following groups and further by a halogen atom, an oxo and/or hydroxy group:

cyano group, nitro group, carboxyl group, sulfo group, $C_{3\text{-}10}$ alkyl group, substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted alkenyl group, $C_{3\text{-}10}$ alkoxy group, substituted alkoxy group, optionally substituted cycloalkoxy group, optionally substituted alkoxycarbonyl group, optionally substituted carbamoyl

group, optionally substituted carbamimidoyl group, optionally substituted alkylthio group, optionally substituted alkylsulfinyl group, optionally substituted alkylsulfonyl group, optionally substituted amino group, optionally substituted sulfamoyl group, optionally substituted alkanoyl group, a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic oxy group is optionally substituted), and a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonyl group is optionally substituted);

R^6, R^7, R^8 and R^9 are independently a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a cyano group, an optionally substituted alkyl group, an optionally substituted alkoxy group, an optionally substituted alkylsulfonyloxy group or an optionally substituted amino group; or

R^6 and R^7, or R^7 and R^8, or R^8 and R^9 may combine at the ends to form an alkylene group which alkylene group may contain 1 to 3 heteroatoms selected independently from nitrogen, sulfur and oxygen atoms, and may have a substituent(s); and

R^{10} is an aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the aromatic ring is optionally substituted), or a pharmaceutically acceptable salt thereof.

The compound (I) of the present invention encompasses a mixture of stereoisomers, respective stereoisomers in a purified or substantially purified form. For example, the compounds of the formula (I) may have

one or more asymmetric carbon atoms and therefore may occur as individual enantiomers or diastereomers, or a mixture thereof. The present compounds include respective isomers and a mixture thereof. In addition, when the compound (I) has a double bond, geometric isomers may occur (cis- and trans-forms), and when the compound (I) has a group containing an unsaturated bond such as carbonyl, tautomeric forms may occur, and the present compounds include respective isomers and a mixture thereof.

Further, the pharmaceutically acceptable salts of compound (I) of the present invention include an intramolecular salt, a hydrate, solvate, or the like.

As used herein, the term "aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" refers to preferably a "5- to 7-membered monocyclic aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" including specifically phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl, oxepinyl and thiepinyl groups, and the like.

The term "saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" refers to preferably a "saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" including specifically the following groups. Examples of 5-membered heterocyclic group include 2H-pyrrolyl, 3H-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, oxazolinyl, oxazolidinyl, thiazolyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, tetrazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, 1,2,3,4-

oxatriazolyl, 1,2,3,5-oxatriazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathiolyl groups, and the like.

Examples of 6-membered heterocyclic group include 2H-pyranyl, 4H-pyranyl, pyridyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-ozathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl groups, and the like.

Examples of 7-membered heterocyclic group include azepinyl, oxepinyl and thiepinyl groups, and the like.

Examples of 8-membered heterocyclic group include azocinyl, oxocinyl and thiocinyl groups, and the like.

As used herein, the heterocyclic moiety of the "saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms", "saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms", and "a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonylamino group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" refers to the aforementioned "saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms".

In such cases where the binding position for these aromatic ring, heterocyclic group, and the like is not specifically defined, the definition is meant to encompass all the possible binding positions. For example, the term "pyridyl group" means 2-, 3- or 4-pyridyl group, and the term "thienyl

group" means 2- or 3-thienyl group. The same is applied to other aromatic rings and heterocyclic groups.

When the saturated or unsaturated monocyclic or bicyclic heterocyclic group, heterocyclic oxy group, heterocyclic carbonyl group and heterocyclic carbonylamino group each containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms have a substituent(s), the substitution includes oxidation of heteroatom(s) in the heterocycle in the respective groups. Specifically, compounds having a heteroatom(s) in the heterocycle of said groups as N-oxide, S-oxide (SO) or S,S-dioxide (SO_2) also fall within the scope of the present invention.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "alkyl group" or "alkyl" means a straight or branched saturated hydrocarbon chain having 1 to 10 carbon atoms and a cyclic saturated hydrocarbon chain having 3 to 10 carbon atoms. As a straight or branched hydrocarbon chain, those having 2 to 10 carbon atoms are preferred and those having 2 to 6 carbons are more preferred. Other preferred examples are straight chain alkyl groups having 1 to 6 carbon atoms, especially those having 1 to 4 carbon atoms. Examples of alkyl group include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl and isohexyl groups, and the like.

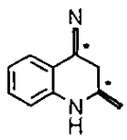
The term "alkoxy group" or "alkoxy" means a straight or branched alkyloxy group having 1 to 10 carbon atoms and a cyclic alkyloxy group having 3 to 10 carbon atoms. As a straight or branched hydrocarbon chain, those having 2 to 10 carbon atoms are preferred and those having 2 to 6 carbons are more preferred. Other preferred examples are straight chain alkoxy groups having 1 to 6 carbon atoms, especially those having 1 to 4 carbon atoms. Examples of alkoxy group include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, tert-pentoxy, hexoxy and isohexoxy groups, and the like.

The term "alkylene group" or "alkylene" means a saturated hydrocarbon chain wherein a hydrogen atom is removed from each of the terminal carbons of a straight hydrocarbon chain. Preferred examples include an alkylene group having 1 to 6 carbon atoms, specifically, methylene, ethylene, trimethylene and tetramethylene groups, and the like. When an alkylene group herein used contains 1 to 3 heteroatoms selected independently from nitrogen, sulfur and oxygen atoms, the term "alkylene" includes a group of the formula:-O-$(CH_2)_m$-O-, -S-$(CH_2)_m$-S-, -NH-$(CH_2)_m$-NH-, or -O-$(CH_2)_m$-NH- (wherein m is an integer of 1 to 4), or the like.

The term "alkanoyl group" or "alkanoyl" means a straight or branched alkylcarbonyl group having 1 to 10 carbon atoms, preferably an alkylcarbonyl group having 1 to 6 carbon atoms, more preferably an alkylcarbonyl group having 1 to 4 carbon atoms. Examples of alkanoyl group include acetyl, propionyl, butyryl, valeryl and pivaloyl groups, and the like.

The term "alkenyl group" or "alkenyl" means a straight or branched hydrocarbon chain having 2 to 10 carbon atoms and containing at least one double bond, preferably an alkenyl group having 2 to 6 carbon atoms, more preferably an alkenyl group having 2 to 4 carbon atoms Examples of alkenyl group include vinyl, 1-propenyl, allyl, isopropenyl, butenyl, butadienyl and pentenyl groups, and the like.

As herein used throughout the claims and specification, when the term "mono- or di-alkyl" refers to di-alkyl, the alkyl moieties may be independent from each other. In addition, a compound of the formula below means that it takes the configuration (2R*,4 S*), wherein (2R*,4S*) refers to a mixture of (2R.4S) and (2S,4R).



The compounds of the present invention have CETP inhibitory

activity and are effective for increasing HDL cholesterol and lowering LDL cholesterol. Accordingly, the said compounds are useful in prevention and/or treatment of diseases such as arteriosclerosis, hyperlipemia, and the like.

BEST MODE FOR CARRYING OUT THE INVENTION

Preferred compounds of the present invention are those wherein R5 is a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms, wherein the heterocyclic group is substituted by 1 to 5 substituents selected from the following groups, or said heterocyclic group is substituted by 1 to 5 substituents selected from the following groups along with halogen atom, oxo and/or hydroxy group:

cyano group, nitro group, carboxyl group, sulfo group, C_{3-10} alkyl group, substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted alkenyl group, C_{3-10} alkoxy group, substituted alkoxy group, optionally substituted cycloalkoxy group, optionally substituted alkoxycarbonyl group, carbamoyl group, optionally substituted mono- or di-alkylcarbamoyl group, optionally substituted carbamimidoyl group, optionally substituted alkylthio group, optionally substituted alkylsulfinyl group, optionally substituted alkylsulfonyl group, amino group, optionally substituted mono- or di-alkylamino group, optionally substituted alkanoylamino group, optionally substituted alkoxycarbonylamino group, optionally substituted alkylsulfonylamino group, optionally substituted mono- or di-alkylcarbamoylamino group, a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonylamino group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonylamino group is optionally substituted), sulfamoyl group, optionally substituted mono- or di-alkyl sulfamoyl

group, optionally substituted alkanoyl group, a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic oxy group is optionally substituted), and a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonyl group is optionally substituted); and

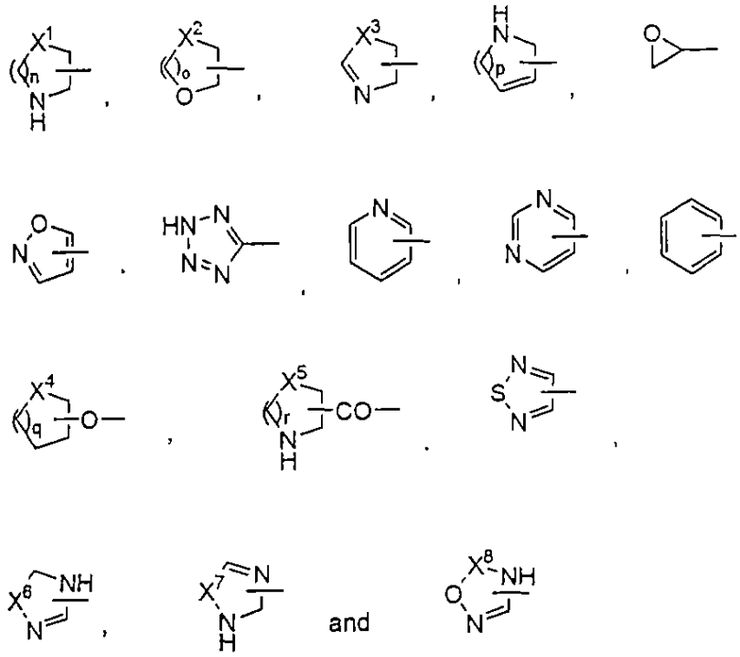
R^{10} is an aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms, which aromatic ring is optionally substituted by 1 to 4 substituents selected from the following groups: halogen atom, carboxyl group, optionally substituted alkoxycarbonyl group, carbamoyl group, optionally substituted mono- or di-alkylcarbamoyl group, optionally substituted alkyl group, optionally substituted alkoxy group, hydroxy group, nitro group, cyano group, amino group, optionally substituted mono- or di-alkylamino group, optionally substituted alkanoyl group, optionally substituted alkylthio group, and a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted).

The substituent(s) for substituted alkyl group, optionally substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted alkenyl group, substituted alkoxy group, optionally substituted alkoxy group, optionally substituted cycloalkoxy group, optionally substituted alkoxycarbonyl group, optionally substituted mono- or di-alkylcarbamoyl group, optionally substituted alkylthio group, optionally substituted alkylsulfinyl group, optionally substituted alkylsulfonyl group, optionally

substituted mono- or di-alkylamino group, optionally substituted alkanoylamino group, optionally substituted alkoxycarbonylamino group, optionally substituted alkylsulfonylamino group, optionally substituted mono- or di-alkylcarbamoylamino group, optionally substituted mono- or di-alkylsulfamoyl group, optionally substituted alkanoyl group, optionally substituted alkylene group, a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonylamino group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonylamino group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic oxy group is optionally substituted), and a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonyl group is optionally substituted) may be 1-5 groups selected from the following groups:

halogen atom; cyano group; hydroxy group; nitro group; carboxyl group; oxo group; thioxo group; sulfo group; cycloalkyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkoxycarbonyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; carbamoyl group; mono- or di-alkylcarbamoyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkyl group optionally substituted by hydroxy

group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkanoyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkoxy group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkanoyloxy group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkylthio group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkylsulfonyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkylsulfinyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; mono- or di-alkylsulfamoyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; amino group; mono- or di-alkylamino group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; mono- or di-alkylsulfamoylamino group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; mono- or di-alkylureido group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; and a group of the formulas:



wherein X^1 and X^3 are independently CH_2, NH, O, S, SO or SO_2, X^2 and X^5 are independently CH_2, O, S, SO or SO_2; X^4 is NH, O, S, SO or SO_2; X^6 and X^7 are independently O or S; X^8 is S or SO; and n, o, p, q and r are independently an integer of 1 to 4, wherein each group of the above formula is optionally substituted by 1 to 3 substituents selected from the following groups:

halogen atom, carboxyl group, hydroxy group, cyano group, oxo group, thioxo group, alkyl group, hydroxyalkyl group, alkoxycarbonylalkyl group, carboxyalkyl group, morpholinylalkyl group, phenylalkyl group, alkanoyl group, hydroxyalkanoyl group, alkoxyalkanoyl group, alkoxy group, phenylalkoxy group, alkoxycarbonyl group, benzyloxycarbonyl group, mono- or di-alkylamino group, mono- or di-alkylcarbamoyl group, mono- or di-alkylsulfamoyl group, alkylsulfonyl group and tetrazolyl group.

Furthermore, the "aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is preferably a phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, furyl,

pyrimidinyl, triazolyl or thienyl group;

The "saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is preferably a morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, hexahydroazepinyl, pyrrolinyl, imidazolidinyl, oxazolidinyl, tetrahydropyranyl, tetrahydrofuranyl, dioxolanyl, oxiranyl, pyrimidinyl, pyridyl, triazolyl, tetrazolyl, oxadiazolyl, dihydropyrimidinyl, pyrazinyl, thiazolyl, oxazolinyl, oxazolyl, pyridazinyl, imidazolinyl, imidazolyl, pyrazinyl, thienyl, pyrrolyl, furyl or dihydrooxazinyl group.

The "saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is preferably a morpholinyloxy, thiomorpholinyloxy piperazinyloxy, pyrrolidinyloxy, piperidinyloxy, hexahydroazepinyloxy, pyrrolinyloxy, imidazolidinyloxy, oxazolidinyloxy, tetrahydropyranyloxy, tetrahydrofuranyloxy, dioxolanyloxy, oxiranyloxy, pyrimidinyloxy, pyridyloxy, triazolyloxy, tetrazolyloxy, oxadiazolyloxy, dihydropyrimidinyloxy, pyrazinyloxy, thiazolyloxy, oxazolinyloxy, oxazolyloxy, pyridazinyloxy, imidazolinyloxy, imidazolyloxy, pyrazinyloxy, thienyloxy, pyrrolyloxy, furyloxy or dihydrooxazinyloxy group.

The "saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is preferably a morpholinylcarbonyl, thiomorpholinylcarbonyl piperazinylcarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, hexahydroazepinylcarbonyl, pyrrolinylcarbonyl, imidazolidinylcarbonyl, oxazolidinylcarbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylcarbonyl, dioxolanylcarbonyl, oxiranylcarbonyl pyrimidinylcarbonyl, pyridylcarbonyl, triazolylcarbonyl, tetrazolylcarbonyl, oxadiazolylcarbonyl, dihydropyrimidinylcarbonyl, pyrazinylcarbonyl, thiazolylcarbonyl, oxazolinylcarbonyl, oxazolylcarbonyl, pyridazinyl-

carbonyl, imidazolinylcarbonyl, imidazolylcarbonyl, pyrazinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl or dihydrooxazinylcarbonyl group.

The "saturated or unsaturated monocyclic or bicyclic heterocyclic carbonylamino group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is preferably a morpholinylcarbonylamino, thiomorpholinylcarbonylamino piperazinylcarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, hexahydroazepinylcarbonylamino, pyrrolinylcarbonylamino, imidazolidinylcarbonylamino, oxazolidinylcarbonylamino, tetrahydropyranylcarbonylamino, tetrahydrofuranylcarbonylamino, dioxolanylcarbonylamino, oxiranylcarbonylamino, pyrimidinylcarbonylamino, pyridylcarbonylamino, triazolylcarbonylamino, tetrazolylcarbonylamino, oxadiazolylcarbonylamino, dihydropyrimidinylcarbonylamino, pyrazinylcarbonylamino, thiazolylcarbonylamino, oxazolinylcarbonylamino, oxazolylcarbonylamino, pyridazinylcarbonylamino, imidazolinylcarbonylamino, imidazolylcarbonylamino, pyrazinylcarbonylamino, thienylcarbonylamino, pyrrolylcarbonylamino, furylcarbonylamino or dihydrooxazinylcarbonylamino group.

In a preferred embodiment of the present invention, R^1 is a hydrogen atom; an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), alkylthio group, alkylsulfonyl group, alkenyl group, amino group, mono- or di-alkylamino group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by 1 to 3 substituents

selected independently from carboxyl group and alkoxycarbonyl group), alkanoylamino group (said alkanoylamino group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, hydroxy group and halogen atom), halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), morpholinyl group optionally substituted by oxo group, piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), and pyrimidinyl group (said pyrimidinyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group); a carbamoyl group optionally substituted by alkoxy group; a dihydrooxazolyl group optionally substituted by 1 to 2 substituents selected independently from carboxyl group, alkoxycarbonyl

group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; a dihydroimidazolyl group optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; a dihydrooxazinyl group optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; mono- or di-alkylcarbamoyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group); an alkyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group); an alkanoyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group,

cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group); a morpholinylcarbonyl group ; a piperazinylcarbonyl group optionally substituted by alkyl group, carboxyalkyl group or alkoxycarbonylalkyl group;

a pyrrolidinylcarbonyl group optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group; or a piperidinylcarbonyl group optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group;

R^5 is a saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms;

wherein said heterocyclic group is substituted by 1 to 4 substituents selected from the following groups, or said heterocyclic group is substituted by 1 to 4 substituents selected from the following groups along with a halogen atom, an oxo and/or hydroxy group:

cyano group;

nitro group;

carboxyl group;

sulfo group;

cycloalkyl group optionally substituted by carboxyl or alkoxycarbonyl group;

C_{3-10} alkyl group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group tetrazolyl

group, mono- or di-alkylcarbamoyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, carboxyl or hydroxy group), alkanoyl group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group optionally substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, dioxolanyl group optionally substituted by alkyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group, morpholinyl group, and piperidinyloxy group optionally substituted by alkyl group;

alkenyl group optionally substituted by a group selected from cyano group, hydroxy group, carboxyl group, benzyloxycarbonyl group, and tetrazolyl group;

alkenyloxy group optionally substituted by carboxyl group;

C_{3-10} alkoxy group;

alkoxy group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by carboxyl, alkoxycarbonyl or hydroxy group), alkoxy group (said alkoxy group is optionally substituted by carboxyl, formyl or hydroxy group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, aminosulfonyl group, amino group, mono- or di-alkylamino group substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally

substituted by morpholinyl group, cycloalkyl group optionally substituted by carboxymethyl group, oxiranyl group, phenyl group optionally substituted by alkoxy or carboxyl group, morpholinyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, pyrrolidinyl group substituted by oxo group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group, pyrimidinyl group, pyridyl group, dioxolanyl group optionally substituted by alkyl group, oxadiazolyl group optionally substituted by oxo group, oxathiadiazolyl group optionally substituted by oxo group, pyrrolidinylcarbonyl group optionally substituted by carboxyl group, piperidinyloxy group optionally substituted by alkyl group, and morpholinylcarbonyl group;

alkoxycarbonyl group optionally substituted by phenyl group;

carbamoyl group;

mono- or di-alkylcarbamoyl group optionally substituted by a group selected from carboxyl group, morpholinyl group and alkoxy group;

hydroxycarbamimidoyl group;

alkylthio group optionally substituted by a group selected from hydroxy group, carboxyl group and mono- or di-alkylcarbamoyl group;

alkylsulfinyl group;

alkylsulfonyl group optionally substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group and mono- or di-alkylcarbamoyl group;

amino group;

mono- or di-alkylamino group optionally substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group and morpholinyl group;

mono- or di-alkanoylamino group optionally substituted by a group selected from hydroxy group, alkoxy group, carboxyl group and amino group;

mono- or di-alkylcarbamoylamino group optionally substituted by alkoxy group;

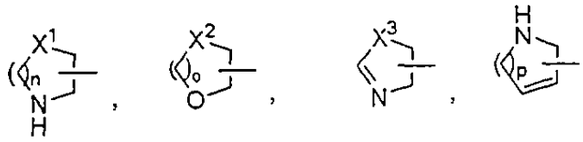
morpholinylcarbonylamino group;

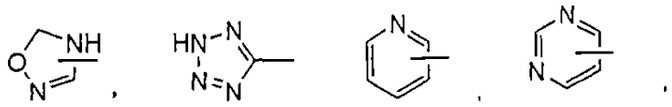
sulfamoyl group;

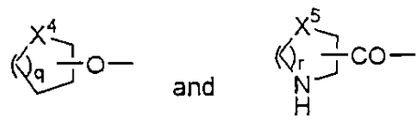
mono- or di-alkylsulfamoyl group;

alkanoyl group optionally substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group and morpholinyl group; or

a group selected from the following groups:







and

wherein X^1 and X^3 are independently CH_2, NH, O, S, SO or SO_2, X^2 and X^5 are independently CH_2, O, S, SO or SO_2; X^4 is NH, O, S, SO or SO_2; and n, o, p, q and r are independently an integer of 1 to 4, wherein each group of the above formula is optionally substituted by a substituent(s) selected from the following groups:

carboxyl group, hydroxy group, cyano group , oxo group, alkyl group, hydroxyalkyl group, alkoxycarbonylalkyl group, carboxyalkyl group, morpholinylalkyl group, phenylalkyl group, alkanoyl group,

hydroxyalkanoyl group, alkoxyalkanoyl group, alkoxy group, phenylalkoxy group, alkoxycarbonyl group, benzyloxycarbonyl group, mono- or di-alkylamino group, mono- or di-alkylcarbamoyl group, mono- or di-alkylsulfamoyl group, alkylsulfonyl group and tetrazolyl group;

R^6, R^7, R^8 and R^9 are independently a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a cyano group, an alkyl group, an alkoxy group, or a mono- or di-alkylamino group, wherein said alkyl, alkoxy and mono- or di-alkylamino groups are optionally substituted by 1 to 6 substituents selected independently from halogen atom, hydroxy group, alkoxy group, alkylthio group, amino group, nitro group, cyano group, oxo group, carboxyl group, alkoxycarbonyl group and mono- or di-alkylamino group; or

R^6 and R^7, or R^7 and R^8, or R^8 and R^9 may combine at the ends to form an alkylene group which alkylene group may contain 1 to 3 heteroatoms selected independently from nitrogen, sulfur and oxygen atoms;

R^{10} is an aromatic monocyclic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms;

wherein the monocyclic aromatic ring is optionally substituted by 1 to 4 substituents selected independently from halogen atom, carboxyl group, alkoxycarbonyl group, carbamoyl group, mono- or di-alkylcarbamoyl group, alkyl group, alkoxy group, hydroxy group, nitro group, cyano group, amino group, mono- or di-alkylamino group, alkanoyl group, alkylthio group, tetrazolyl group and dihydrooxazolyl group, wherein the alkyl, alkoxy, mono- or di-alkylamino, mono- or di-alkylcarbamoyl, alkanoyl and alkylthio groups are optionally substituted by a substituent(s) selected independently from halogen atom, and hydroxy, alkoxy, amino, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, alkylpiperazinyl and alkanoylpiperazinyl groups.

Furthermore, in the preferred compounds, the "aromatic monocyclic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a phenyl group, a pyridyl group, a pyrimidinyl group, a furyl group or a thienly group; and the "saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a pyrimidinyl group, a pyridyl group, a triazolyl group, a tetrazolyl group, a oxadiazolyl group, a dihydropyrimidinyl group, a pyrazinyl group, a thiazolyl group, an oxazolyl group, an imidazolyl group, a dihydrooxazinyl group, a dihydropyrazinyl group or a pyrazolyl group.

In more preferred compounds, R^1 is a hydrogen atom; an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), alkylthio group, alkylsulfonyl group, alkenyl group, amino group, mono- or di-alkylamino group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group and alkoxycarbonyl group), alkanoylamino group (said alkanoylamino group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, hydroxy group and halogen atom), halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), phenyl group (said

phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), morpholinyl group optionally substituted by oxo group, piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group), pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), and pyrimidinyl group (said pyrimidinyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group); dihydrooxazolyl group optionally substituted by 1 to 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; or a mono- or di-alkylcarbamoyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom,

amino group and hydroxy group);

R^2 is an alkyl group;

R^3 is a hydrogen atom;

R^4 is an alkylene group;

R^5 is a heterocyclic group selected from pyrimidinyl group, pyridyl group, triazolyl group, tetrazolyl group, oxadiazolyl group, dihydropyrimidinyl group, pyrazinyl group, thiazolyl group, oxazolyl group, imidazolyl group, dihydrooxazinyl group, pyrazolyl group and dihydropyrazinyl group, wherein said heterocyclic group is substituted by 1 to 4 substituents selected from the following groups, or 1 to 4 substituents selected from the following groups and oxo group:

cyano group;

nitro group;

carboxyl group;

sulfo group;

C_{3-10} alkyl group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, tetrazolyl group, mono- or di-alkylcarbamoyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, carboxyl or hydroxy group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group optionally substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, dioxolanyl group optionally substituted by alkyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl

or carboxyalkyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group, morpholinyl group, and piperidinyloxy group optionally substituted by alkyl group;

alkenyl group optionally substituted by a group selected from cyano group, hydroxy group, carboxyl group, benzyloxycarbonyl group, and tetrazolyl group;

alkenyloxy group optionally substituted by carboxyl group;

C_{3-10} alkoxy group;

alkoxy group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group optionally substituted by hydroxy group, alkoxy group optionally substituted by carboxyl or hydroxy group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, aminosulfonyl group, amino group, mono- or di-alkylamino group substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, cycloalkyl group optionally substituted by carboxymethyl group, oxiranyl group, phenyl group optionally substituted by alkoxy or carboxyl group, morpholinyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, pyrrolidinyl group optionally substituted by oxo group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group, pyrimidinyl group, pyridyl group, dioxolanyl group optionally substituted by alkyl group, oxadiazolyl group optionally substituted by oxo group, oxathiadiazolyl group optionally substituted by oxo group, pyrrolidinylcarbonyl group

optionally substituted by carboxyl group, piperidinyloxy group optionally substituted by alkyl group, and morpholinylcarbonyl group;
alkoxycarbonyl group optionally substituted by phenyl group;
carbamoyl group;
mono- or di-alkylcarbamoyl group optionally substituted by a group selected from carboxyl group, morpholinyl group and alkoxy group;
hydroxycarbamimidoyl group;
alkylthio group optionally substituted by a group selected from hydroxy group, carboxyl group and mono- or di-alkylcarbamoyl group;
alkylsulfinyl group;
alkylsulfonyl group optionally substituted by a group selected from hydroxy group, carboxyl group and mono- or di-alkylcarbamoyl group;
amino group;
mono- or di-alkylamino group optionally substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group and morpholinyl group;
alkanoylamino group optionally substituted by a group selected from hydroxy group, alkoxy group, carboxyl group and amino group;
mono- or di-alkylureido group optionally substituted by alkoxy group;
morpholinylcarbonylamino group;
sulfamoyl group;
mono- or di-alkylsulfamoyl group;
morpholinyl group optionally substituted by a group selected from oxo group and carboxyl group;
optionally oxidized thiomorpholinyl group;
piperazinyl group optionally substituted by a group selected from cyano group, alkyl group, hydroxyalkyl group, alkoxycarbonylalkyl group, carboxyalkyl group, alkanoyl group, hydroxyalkanoyl group, alkoxyalkanoyl group, benzyloxycarbonyl group, mono- or di-alkylcarbamoyl group, mono- or di-alkylsulfamoyl group, alkylsulfonyl

group and tetrazolyl group;

piperidinyl group optionally substituted by a group selected from carboxyl group, hydroxy group, oxo group, alkyl group, hydroxyalkyl group, carboxyalkyl group, alkanoyl group, alkoxy group, phenylalkoxy group, alkoxycarbonyl group and alkoxycarbonylalkyl group;

pyrrolidinyl group optionally substituted by a group selected from oxo group, carboxyl group, alkanoyl group and mono- or di-alkylamino group;

pyrrolinyl group optionally substituted by oxo group;

hexahydrodiazepinyl group optionally substituted by alkanoyl group;

diazolidinyl group optionally substituted by oxo group;

dioxolanyl group optionally substituted by alkyl group;

pyridyl group optionally substituted by carboxyl group, hydroxy group or hydroxyalkyl group (said pyridyl group is optionally further oxidized);

tetrazolyl group substituted by hydroxy group or alkyl group that is optionally substituted by morpholinyl group;

dihydrooxadiazolyl group optionally substituted by oxo group;

dihydroimidazolyl group;

dihydrooxazolyl group;

oxazolidinyl group optionally substituted by oxo group;

tetrahydropyridyl group optionally substituted by benzyl group;

pyrimidinyl group;

tetrahydropyranyl group;

piperidinyloxy group optionally substituted by a group selected from alkyl group, carboxyl group, carboxyalkyl group and alkanoyl group;

pyrrolidinyloxy group optionally substituted by a group selected from alkyl group, carboxyl group, carboxyalkyl group and alkanoyl group;

tetrahydropyranyloxy group;

tetrahydrofuranyloxy group;

optionally oxidized thianyloxy group;

morpholinylcarbonyl group;

piperazinylcarbonyl group optionally substituted by a group selected from alkanoyl group and alkyl group; and

pyrrolidinylcarbonyl group;

R^6 and R^9 each are a hydrogen atom;

R^7 and R^8 are independently a hydrogen atom, an alkyl group optionally substituted by halogen atom, an alkoxy group, a mono- or di-alkylamino group or halogen atom; or

R^7 and R^8 combine at the ends to form an alkylenedioxy group; and

R^{10} is a phenyl or pyridyl group, which phenyl or pyridyl group is optionally substituted by 1 to 4 substituents selected from alkyl group optionally substituted by halogen atom, alkoxy group, hydroxy group, halogen atom, cyano group, amino group and mono- or di-alkylamino group.

In further preferred compounds, R^1 is an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group and alkoxycarbonyl group), alkenyl group, halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), and pyrrolidinyl group

(said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group); or a dihydrooxazolyl group optionally substituted by 1 or 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group;

R^5 is a pyrimidinyl group, a pyridyl group, a triazolyl group, a tetrazolyl group, an oxadiazolyl group, a dihydropyrimidinyl group, a pyrazinyl group, a thiazolyl group, an oxazolyl group, a dihydrooxazinyl group, a pyrazolyl group or a dihydropyrazinyl group, said group being substituted by 1 to 4 substituents selected from the following groups:

cyano group;

nitro group;

carboxyl group;

sulfo group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group optionally substituted by carboxyl or hydroxy group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkenyl group optionally substituted by carboxyl group, cyano group or benzyloxycarbonyl group;

alkoxy group substituted by a group selected from halogen atom,

cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group optionally substituted by carboxyl or hydroxy group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkoxycarbonyl group optionally substituted by phenyl group;

mono- or di-alkylcarbamoyl group optionally substituted by carboxy group;

hydroxycarbamimidoyl group;

alkylthio group;

alkylsulfinyl group;

alkylsulfonyl group optionally substituted by carboxyl group;

mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group or morpholinyl group;

mono- or di-alkylsulfamoyl group;

morpholinyl group;

optionally oxidized thiomorpholinyl group;

piperazinyl group optionally substituted by a group selected from alkyl group, alkanoyl group and hydroxyalkanoyl group;

piperidinyl group optionally substituted by a group selected from carboxyl group, alkyl group and alkoxycarbonyl group;

dioxolanyl group optionally substituted by alkyl group;

tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl

group or morpholinylalkyl group;

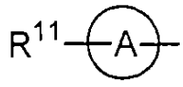
dihydrooxadiazolyl group optionally substituted by oxo group;

pyrimidinyl group; or

tetrahydropyranyl group; and

R^{10} is a phenyl or pyridyl group, which phenyl or pyridyl group is optionally substituted by 1 to 4 substituents selected from alkyl group optionally substituted by halogen atom, alkoxy group, hydroxy group, halogen atom, cyano group, amino group and mono- or di-alkylamino group.

Another embodiment of the present invention include compounds of the formula (I) wherein R^5 is a group of the formula:



wherein Ring A is a saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms, and

R^{11} is a group selected from the following groups:

cyano group;

nitro group;

carboxyl group;

sulfo group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, hydroxy or carboxyl group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group

optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkenyl group optionally substituted by carboxyl group, cyano group or benzyloxycarbonyl group;

alkoxy group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, hydroxy or carboxyl group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkoxycarbonyl group optionally substituted by phenyl group;

mono- or di-alkylcarbamoyl group optionally substituted by carboxyl group;

hydroxycarbamimidoyl group;

alkylthio group;

alkylsulfinyl group;

alkylsulfonyl group optionally substituted by carboxyl group;

mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group or morpholinyl group;

mono- or di-alkylsulfamoyl group;

morpholinyl group;

optionally oxidized thiomorpholinyl group;

piperazinyl group optionally substituted by a group selected from alkyl

group, alkanoyl group and hydroxyalkanoyl group;

pyrrolidinyl group optionally substituted by carboxyl group, carboxyalkyl group, alkyl group, alkoxycarbonyl group or alkoxycarbonylalkyl group;

piperidinyl group optionally substituted by carboxyl group, carboxyalkyl group, alkyl group, alkoxycarbonyl group or alkoxycarbonylalkyl group;

dioxolanyl group optionally substituted by alkyl group;

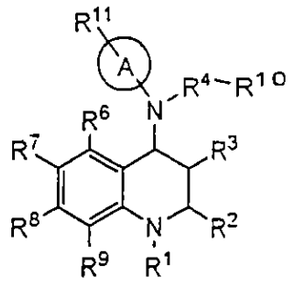
tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl group or morpholinylalkyl group;

dihydrooxadiazolyl group optionally substituted by oxo group;

pyrimidinyl group, or

tetrahydropyranyl group;

which compound is shown by the formula (I-A):



(I-A)

wherein each symbol has the same meaning as defined above.

More preferred embodiment includes compounds of the formula (I) wherein R^1 is a hydrogen atom; an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), alkylthio group, alkylsulfonyl group, alkenyl group, amino group, mono- or di-alkylamino group,

tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group and alkoxycarbonyl group) , alkanoylamino group (said alkanoylamino group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, hydroxy group and halogen atom), halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), morpholinyl group optionally substituted by oxo group, piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group), pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), and pyrimidinyl group (said pyrimidinyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group); dihydrooxazolyl group optionally substituted

by 1 to 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; or a mono- or di-alkylcarbamoyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group);

R^2 is an alkyl group;

R^3 is a hydrogen atom;

R^4 is an alkylene group;

Ring A and R'' are the same groups as defined above;

R^6 and R^9 each are a hydrogen atom;

R^7 and R^8 are independently a hydrogen atom, an alkyl group optionally sbustituted by halogen atom, alkoxy group, or mono- or di-alkylamino group; or combine at the ends to form an alkylenedioxy group; and

R^{10} is a phenyl or pyridyl group, which phenyl or pyridyl group is optionally substituted by 1 to 4 substituents selected from alkyl group optionally substiuted by halogen atom, alkoxy group, hydroxy group, halogen atom, cyano group, amino group and mono- or di-alkylamino group.

Another preferred embodiment includes compounds of the formula (I) wherein Ring A is a saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms, and

R^{11} is a group selected from the followings groups:

cyano group; nitro group; carboxyl group; sulfo group; alkyl group substituted by a group selected from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group optionally substituted by phenyl or hydroxy group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group; alkenyl group optionally substituted by carboxyl group or benzyloxycarbonyl group; alkoxy group substituted by carboxyl group, hydroxy group, alkoxy group, alkylthio group, alkylsulfonyl group or alkoxyphenyl group; alkoxycarbonyl group optionally substituted by phenyl group; mono- or di-alkylcarbamoyl group optionally substituted by carboxyl group; hydroxycarbamimidoyl group; alkylthio group; alkylsulfinyl group; alkylsulfonyl group optionally substituted by alkoxycarbonyl group; mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group or morpholinyl group; mono- or di-alkylsulfamoyl group; morpholinyl group; optionally oxidized thiomorpholinyl group; piperazinyl group optionally substituted by a group selected from alkyl group, alkanoyl group and hydroxyalkanoyl group; piperidinyl group optionally substituted by carboxyl group, alkyl group or alkoxycarbonyl group; dioxolanyl group optionally substituted by alkyl group; tetrazolyl group substituted by alkyl group, hydroxyalkyl group or morpholinylalkyl group; dihydrooxadiazolyl group optionally substituted by oxo group; pyrimidinyl group; or tetrahydropyranyl group.

More preferred embodiment herein includes compounds of the formula (I) wherein R^1 is an alkoxycarbonyl group optionally subsututed by

a group selected from hydroxy group and alkoxy group; or a dihydrooxazolyl group optionally substituted by hydroxyalkyl group;

R^2 is an alkyl group;

R^3 is a hydrogen atom;

R^4 is an alkylene group;

Ring A and R^{11} are the same groups as defined above;

R^6 and R^9 each are a hydrogen atom; and

R^7 and R^8 are independently a hydrogen atom, an alkyl group optionally sbustituted by 1 to 9 halogen atoms, an alkoxy group, or a mono- or di-alkylamino group; or combine at the ends to form an alkylenedioxy group;

R^{10} is a phenyl or pyridyl group, which phenyl or pyridyl group is optionally substituted by 1 to 4 substituents selected from alkyl group optionally substiuted by 1 to 9 halogen atoms, alkoxy group, hydroxy group, halogen atom, cyano group, amino group and mono- or di-alkylamino group.

Examples of Ring A include a pyrimidinyl group, a pyridyl group, a triazolyl group, a tetrazolyl group, an oxadiazolyl group, a dihydropyrimidinyl group, a pyrazinyl group, a thiazolyl group, an oxazolyl group, a dihydrooxazinyl group, an imidazolyl group, a pyrazolyl group, a dihydropyrazinyl group, and the like.

More preferred compounds include those wherein Ring A is a pyrimidinyl group, a pyridyl group, a tetrazolyl group, an oxadiazolyl group, a pyrazinyl group, a thiazolyl group or an oxazolyl group; and

R^{11} is a carboxyl group; a cyano group; a nitro group; an alkyl group substituted by a group selected from hydroxy group, cyano group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, hydroxyalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by carboxyl

group, piperidinyl group optionally substituted by carboxyl group, piperazinyl group optionally substituted by alkyl group and morpholinyl group; an alkenyl group optionally substituted by carboxyl group; an alkoxy group substituted by a group selected from hydroxy group, cyano group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, hydroxyalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by carboxyl group, piperidinyl group optionally substituted by carboxyl group, piperazinyl group optionally substituted by alkyl group and morpholinyl group; an alkoxycarbonyl group; a hydroxycarbamimidoyl group; alkylthio group; an alkylsulfonyl group optionally substituted by carboxyl group; a mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group, alkoxy group or mono- or di-alkylamino group; a morpholinyl group; an optionally oxidized thiomorpholinyl group; a piperazinyl group optionally substituted by a group selected from alkyl group, alkanoyl group and hydroxyalkanoyl group; a pyrrolidinyl group optionally substituted by carboxyl group, alkyl group carboxyalkyl group or alkoxycarbonyl group; a piperidinyl group optionally substituted by carboxyl group, alkyl group, carboxyalkyl group or alkoxycarbonyl group; a tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl group, or morpholinylalkyl group; an oxodihydrooxadiazolyl group; a pyrimidinyl group; or a tetrahydropyranyl group.

Still more preferred compounds include those wherein R^1 is an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom,

carboxyl group and alkoxycarbonyl group), alkenyl group, halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), and pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group); or a dihydrooxazolyl group optionally substituted by 1 or 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group;

R^{10} is a phenyl group substituted by 1 to 3 substituents selected from alkyl group optionally substituted by halogen atom, alkoxy group, halogen atom and cyano group;

Ring A is a pyrimidinyl group, a pyridyl group, a tetrazolyl group, an oxadiazolyl group or a thiazolyl group; and

R^{11} is a carboxyl group; a cyano group; a nitro group; an alkyl group substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, piperazinyl group

optionally substituted by alkyl group and morpholinyl group; an alkenyl group optionally substituted by carboxyl group; an alkoxy group substituted by a group selected from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, piperazinyl group optionally substituted by alkyl group and morpholinyl group; a hydroxycarbamimidoyl group; an alkylthio group; an alkylsulfonyl group optionally substituted by alkoxycarbonyl group; a mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group or alkoxy group; a morpholinyl group; optionally oxidized thiomorpholinyl group; a piperazinyl group optionally substituted by a group selected from alkyl group, alkanoyl group and hydroxyalkanoyl group; a pyrrolidinyl group optionally substituted by carboxyl group, alkyl group carboxyalkyl group or alkoxycarbonyl group; a piperidinyl group optionally substituted by carboxyl group, alkyl group, carboxyalkyl group or alkoxycarbonyl group; a tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl group, or morpholinylalkyl group; an oxodihydrooxadiazolyl group; a pyrimidinyl group; or a tetrahydropyranyl group.

Still furthermore preferred compounds include those wherein R^1 is an alkoxycarbonyl group optionally substituted by 1 or 5 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, hydroxy group and cycloalkyl group;

R^{10} is a phenyl group substituted by 1 to 3 substituents selected from cyano group, alkyl group optionally substituted by halogen atom and alkoxy group;

Ring A is a pyrimidinyl group, a pyridyl group, a tetrazolyl group or an oxadiazolyl group;

R^{11} is a carboxyl group; an alkyl group substituted by hydroxy group, carboxyl group, alkoxy group or alkylsulfonyl group; an alkenyl group optionally substituted by carboxyl group; an alkoxy group substituted by cyano group, carboxyl group, hydroxy group, alkoxy group, alkylthio group or alkylsulfonyl group; a mono- or di-alkylamino group optionally substituted by carboxyl group or alkoxy group; a morpholinyl group; a piperidinyl group substituted by carboxyl group; or a tetrazolyl group substituted by hydroxyalkyl group;

R^7 is an alkyl group optionally sbustituted by halogen atom, alkoxy group, or mono- or di-alkylamino group; and

R^8 is a hydrogen atom.

Especially preferred compounds include those wherein R^1 is an ethoxycarbonyl group, a hydroxyethoxycarbonyl group, a 2-fluoroethoxycarbonyl group, a 2,2-difluoroethoxycarbonyl group or a 2,2,2-trifluoroethoxycarbonyl group; R^2 is an ethyl group; R^{10} is a phenyl group substituted by 1 to 2 substituents selected from cyano group, trifluoromethyl group and methoxy group; R^7 is a trifluoromethyl group or a methoxy group. In this regared, other examples of especially preferred compounds include those wherein R^1 is a carboxy(C_{2-10}alkoxy)carbonyl group or an alkoxycarbonyl(C_{2-10}alkoxy)carbonyl group, and R^2, R^{10} and R^7 are the same above.

Especially more preferred compounds include those wherein R^1 is an ethoxycarbonyl group or a hydroxyethoxycarbonyl group; R^2 is an ethyl group; R^{10} is a phenyl group substituted by 1 to 2 substituents selected from cyano group, trifluoromethyl group and methoxy group; R^7 is a trifluoromethyl group or a methoxy group.

Most preferred compounds include those listed below.

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-[[3,5-Bis(trifluoromethyl)benzyl]-(5-{[methyl-(2-methoxyethyl)]-amino}pyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-carboxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-carboxyethyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[2-(2-hydroxyethyl)-2H-tetrazol-5-yl]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3,5-Dimethoxybenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3,5-Dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R*,4S*)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[2-(2-hydroxyethyl)-2H-tetrazol-5-yl]pyrimidin-2-yl})amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-hydroxyethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-methanesulphonylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-carboxyethyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-[[3,5-Bis(trifluoromethyl)benzyl]-(5-{[methyl-(2-carboxyethyl)]amino}pyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[3-(tetrazol-5-yl)-propoxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxybutoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-

carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(5-carboxypentyloxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-carboxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxymethylpyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxybutoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(4-carboxybutoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl) benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl) benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-dimethylamino-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl) benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl) benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-

quinoline-1-carboxtlic acid ethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(3-carboxypropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-

carboxylic acid 5-carboxypentyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester; or
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;or
a pharmaceutically acceptable salt thereof.

Further examples of most preferrred compounds include:
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester; or

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester ;

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or a pharmaceutically acceptable salt thereof.

The present compound (I) or a pharmaceutically acceptable salt thereof can be administered either orally or parenterally, and can be formulated into pharmaceutical preparations with a conventional pharmaceutically acceptable carriers used therefor.

The pharmaceutically acceptable salts of the compound (I) may include, for example, alkali metal salts such as lithium, sodium or potassium salt; alkali earth metal salts such as calcium or magnesium salt; salts with zinc or aluminum; salts with organic bases such as ammonium, choline, diethanolamine, lysine, ethylenediamine, tert-butylamine, tert-octylamine, tris(hydroxymethyl)aminomethane, N-methylglucosamie, triethanolamine or dehydroabiethylamine; salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid or phosphoric acid; salts with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid or toluenesulfonic acid; or salts derived from acidic amino acids such as aspartic acid or glutamic acid.

Additionally, the pharmaceutically acceptable salts of the compound (I) may include, for example, quaternary salts formed between a compound of the formula (I) and an alkyl halide or phenylalkyl halide.

Preferred pharmaceutical preparations for oral administration of the present compound (I) or a pharmaceutically acceptable salt thereof include solid formulations such as tablets, granules, capsules or powders; and liquid formulations such as solutions, suspensions or emulsions. Preferred pharmaceutical preparations for parenteral administration include injections or infusions formulated with injectable distilled-water, physiological saline or aqueous glucose solution; suppository; or inhalation preparation.

These pharmaceutical preparations comprise a compound (I) of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier which is usually used for oral or parenteral administration. The pharmaceutically acceptable carriers for oral administration include, for example, a binder (syrup, gum acacia, gelatin, sorbit, tragacanth, polyvinylpyrrolidone, and the like), an excipient (lactose, sugar, cornstarch, potassium phosphate, sorbit, glycine, and the like), a lubricant (magnesium stearate, talc, polyethylene glycol, silica, and the like), a disintegrant (potato starch, and the like), and a wetting agent (anhydrous sodium lauryl sulfate , and the like). The pharmaceutically acceptable carriers for parenteral administration include, for example, injectable distilled-water, physiological saline and aqueous glucose solution.

The dose of a compound (I) of the present invention or a pharmaceutically acceptable salt thereof varies depending on the administration route, age, body weight, disease, and condition/severity, of the patient. It however can usually be in the range of about 0.001 - 1,000 mg/kg/day, preferably in the range of about 0.01 - 100 mg/kg/day, more preferably in the range of about 0.1 - 10 mg/kg/day.

The compounds of the present invention have an inhibitory activity against CETP and show effects of increasing HDL cholesterol and lowering LDL cholesterol. Accordingly, they are useful in the prophylaxis or treatment of a subject (particularly, mammal including human) suffering from arteriosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesteremia, hypertriglyceridemia, familial-hypercholesteremia, cardiovascular diseases, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, restenosis after angioplasty, hypertension, cerebral infarction, cerebral stroke, diabetes, vascular complication of diabetes, thrombotic diseases, obesity, endotoxemia, or the like.

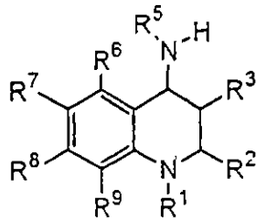
In addition, the compounds of the present invention may be used in combination with other drugs useful for treatment of these diseases. For example, a compounds of the present invention may be used in combination with an inhibitor of cholesterol synthesis such as HMG-CoA reductase inhibitor, an inhibitor of cholesterol absorption such as anion exchange resin, fibrates, a triglyceride lowering agent such as niacin or other cholesterol reducer such as ACAT inhibitor.

The compounds of the present invention are characterized by that an amino group substituted by a heterocycle having a substituent(s) as defined above is introduced into the 4-position of tetrahydroquinoline skeleton, whereby they can exhibit an excellent inhibitory activity against CETP and have an improved bioavailability. Above all, compounds having a carboxyl group at the terminal position of resepctive substituents R^1 - R^{11}, especially those having a carboxyl group at the terminal position of R^1 and/or R^5, or R^1 and/or R^{11} are preferred.

The compound (I) of the present invention can be prepared by the following methods.

PROCESS 1

The compound (I) of the present invention can be prepared by condensing a compound of the formula (II):



(II)

wherein the symbols have the same meaning as defined above with a compound of the formula (III):

R^{10}-R^4-Z^1 (III)

wherein Z^1 is a leaving group and the other symbols have the same meaning as defined above.

The condensation can be carried out in the presence of a base in a suitable solvent.

The leaving group includes a halogen atom including chlorine atom, bromine atom, iodine atom, and a substituted sulfonyloxy group including methanesulfonyloxy group, p-toluenesulfonyloxy group, trifluoromethanesulfonyloxy group.

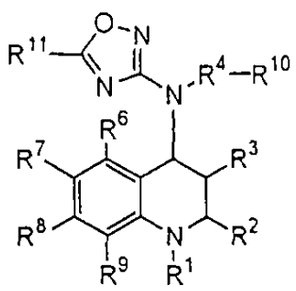
A conventional base can be used as the base, and for example, alkaline metal hydride including sodium hydride, potassium hydride; alkaline metal hydroxide including sodium hydroxide, potassium hydroxide; alkaline earth metal hydroxide including barium hydroxide; alkaline metal alkoxide including sodium methoxide, sodium ethoxide, potassium ethoxide, potassium tert-butoxide; alkaline metal carbonate including sodium carbonate, potassium carbonate, cesium carbonate; alkaline metal bicarbonate including sodium bicarbonate, potassium bicarbonate; amines including triethylamine, diisopropylethylamine, methylpiperidine, dimethylaniline, 1,8-diazabicyclo[5.4.0]undecene, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[4.3.0]nonene; pyridines including pyridine, dimethylaminopyridine can be preferably used.

Any solvent which dose not disturb the reaction can be preferably used, and such a solvent includes, for example, hydrocarbons including pentane, hexane; aromatic hydrocarbons including benzene, toluene, nitrobenzene; halogenated hydrocarbons including dichloromethane, chloroform; ethers including diethylether, tetrahydrofuran; amides including dimethylformamide, N-methylpyrrolidone, 1,3-dimethyl-imidazolidin-2-one; sulfoxides including dimethylsulfoxide; alcohols including methanol, ethanol; esters including ethyl acetate, butyl acetate; ketones including acetone, methyl ethyl ketone; nitriles including acetonitrile; water, or a mixed solvent thereof.

The reaction is carried out from under cooling to under heating, preferably from -78°C to 200°C, more preferably from -30°C to 100°C.

PROCESS 2

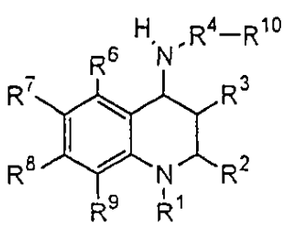
Among the compound of the formula (I-A), a compound of the formula (I-b):



(I-b)

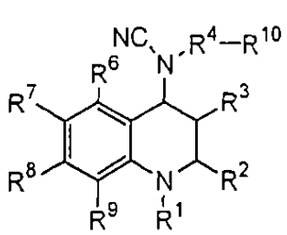
wherein the symbols have the same meaning as defined above can be prepared by

(a) cyanating a compound of the formula (IV):



(IV)

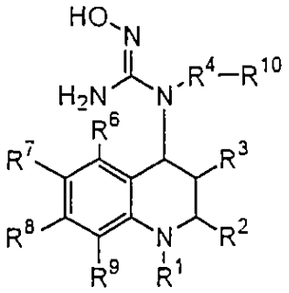
wherein the symbols have the same meaning as defined above to provide a compound of the formula (V):



(V)

wherein the symbols have the same meaning as defined above,

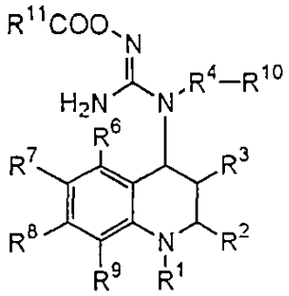
(b) reacting the compound (V) with hydroxylamine or a salt thereof to provide a compound of the formula (VI):



(VI)

wherein the symbols have the same meaning as defined above,

(c) alkanoylating the compound (VI) to provide a compound of the formula (VII):



(VII)

wherein the symbols have the same meaning as defined above, and further

(d) cyclizing the compound (VII) with a base.

The cyanation in the process (a) can be carried out by reacting a halogenated cyanogen in the presence of a base in a suitable solvent.

Cyanogen bromide is preferable as the halogenated cyanogen.

A conventional base can be preferably used as the base, and alkaline metal carbonate including potassium carbonate, or alkaline metal bicarbonate including sodium bicarbonate can be preferably used.

Any solvent which dose not disturb the reaction can be used and the solvent referred to in the PROCESS 1 can be preferably used.

The reaction with hydroxylamine in the process (b) can be carried out in the presence of a base in a suitable solvent.

Tertiary alkylamines including triethylamine, diisopropylethylamine, and the like can be preferably used as the base.

Any solvent which dose not disturb the reaction can be used and the

solvent referred to in the PROCESS 1 can be preferably used.

The alkanoylation in the process (c) can be carried out with an alkanoyl halide in the presence of a base in a suitable solvent.

A conventional base can be used as the base, and amines including triethylamine or diisopropylethylamine, or pyridines including pyridine, 4-dimethylaminopyridine can be preferably used.

Any solvent which dose not disturb the reaction can be used and the solvent referred to in the PROCESS 1 can be preferably used.

In the cyclization in the process (d), a conventional base can be used as the base, and amines including triethylamine or diisopropylethylamine; pyridines including pyridine, 4-dimethylaminopyridine; or alkaline metal alkoxide including sodium methoxide can be preferably used.

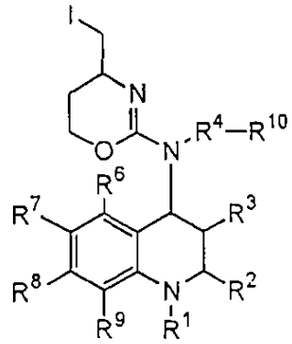
Any solvent which dose not disturb the reaction can be used and the solvent referred to in the PROCESS 1 can be preferably used.

Additionally, the cyclization following the alkanoylating can also be carried out in situ.

The reaction is carried out from under cooling to under heating, preferably from -50°C to 100°C, more preferably from 0°C to 50°C.

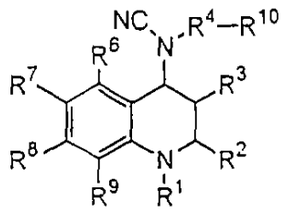
PROCESS 3

Among the compound of the formula (I-A), a compound of the formula (I-c):



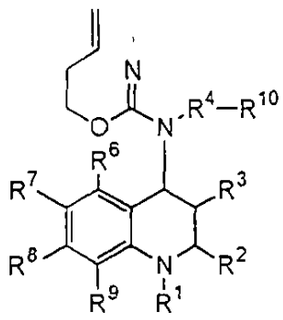
(I-c)

wherein the symbols have the same meaning as defined above can be prepared by reacting a compound of the formula (V):



(V)

wherein the symbols have the same meaning as defined above with 3-buten-1-ol to provide a compound of the formula (VIII):



(VIII)

wherein the symbols have the same meaning as defined above, followed by cyclizing the resulting compound in the presence of iodine, N-iodosuccinimide, or the like.

The reaction with 3-buten-1-ol can be carried out in the presence of a base in a suitable solvent.

Any base which dose not disturb the reaction can be used and the base referred to in the PROCESS 1 can be preferably used.

Any solvent which dose not disturb the reaction can be used and the solvent referred to in the PROCESS 1 can be preferably used.

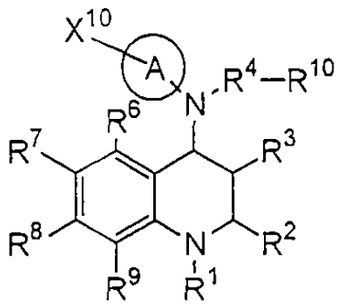
In the cyclization any solvent which dose not disturb the reaction can be used and the solvent referred to in the PROCESS 1 can be preferably used.

The reaction is carried out from under cooling to under heating, preferably from -50°C to 100°C, more preferably from 0°C to 50°C

PROCESS 4

The compound of the formula (I-A) can also be prepared by the

following methods with a compound of the formula (IX):



(IX)

wherein X^{10} is a hydrogen atom, a halogen atom or a hydroxy group and the other symbols have the same meaning as defined above.

In each process of following (A) to (K), unless otherwise specified, the base referred to in the PROCESS 1 can be preferably used as the base.

Additionally, in each process of following (A) to (K) a conventional acid can be used as an acid, and unless otherwise specified, a mineral acid including hydrochloric acid, nitric acid, sulfuric acid; an organic acid represented by sulfonic acids (e.g., methanesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid, and the like) can be preferably used.

Additionally, in each process of following (A) to (K), any solvent which dose not disturb the reaction can be used as the solvent, and specifically, the solvent referred to in the PROCESS 1 can be preferably used.

The leaving group includes a halogen atom including chlorine atom, bromine atom, iodine atom, and a substituted sulfonyloxy group including methanesulfonyloxy group, and trifluoromethanesulfonyloxy group, toluenesulfonyloxy group.

(A) The compound wherein Ring A is a tetrazolyl group and R^{11} is an alkyl group having 3 to 10 carbon atoms or a substituted alkyl group can be prepared by alkylating a compound of the formula (IX) wherein Ring A is a tetrazolyl group and X^{10} is a hydrogen atom.

The alkylation can be carried out by reacting a starting compoumd with a compound of the formula:

R^{11A}-Z^3

wherein R^{11A} is an alkyl group having 3 to 10 carbon atoms or a substituted alkyl group and Z^2 refers to a leaving group in a suitable solvent in the presence or absence of a base, or reacting with a compound of the formula:

R^{11A}-OH

wherein the symbol has the same meaning as defined above in a suitable solvent in the presence of phosphines and azodicarboxylic esters.

The reaction proceeds more preferably when a catalytic amount of an alkaline metal iodide (e.g., potassium iodide, and the like) is added.

Both phosphines and azodicarboxylic esters which usually employed in Mitsunobu reaction can be preferably used. Phosphines include, for example, triphenylphosphine, tributylphosphine, and the like, and azodicarboxylic esters include diethyl azodicarboxylate, diisopropyl azodiformate, and the like.

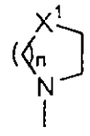
(B) The compound wherein Ring A is 2-oxodihydropyrimidinyl group and R^{11} is an alkyl group having 3 to 10 carbon atoms or a substituted alkyl group can be prepared by alkylating a compound of the formula (IX) wherein Ring A is 2-hydroxypyrimidinyl group and X^{10} is a hydrogen atom with a compound of the formula:

R^{11A}-Z^2

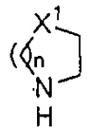
wherein the symbols have the same meaning as defined above.

The reaction can be carried out in the same manner as (A).

(C) The compound wherein R^{11} is an optionally substituted amino group or a group of the formula:



wherein the symbols have the same meaning as defined above can be prepared by reacting a compound of the formula (IX) wherein X^{10} is a halogen atom with a corresponding amine or a compound of the formula:



wherein the symbols have the same meaning as defined above.

The reaction can be carried out in the presence or absence of a base, and in the presence or absence of a palladium catalyst in a suitable solvent.

As the palladium catalyst, a conventional palladium catalyst including palladium acetate, tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, dichlorobis(triphenylphosphine)-palladium, dichlorobis(tri-o-tolylphosphine)palladium, bis-(triphenylphosphine)palladium acetate, or the like can be used.

As the base, alkaline metal hydroxide including sodium hydroxide, potassium hydroxide; alkaline earth metal hydroxide including barium hydroxide; alkaline metal alkoxide including sodium methoxide, sodium ethoxide, potassium ethoxide, potassium tert-butoxide; alkaline metal carbonate including sodium carbonate, potassium carbonate, cesium carbonate; alkaline metal bicarbonate including sodium bicarbonate, potassium bicarbonate; alkaline metal phosphate including potassium phosphate; amines including triethylamine, diisopropylethylamine, methylpiperidine, dicyclohexylmethylamine; and pyridines including pyridine, 4-dimethylaminopyridine can be preferably used.

Additionally, phosphines may be added in the present reaction. As the phosphines, triphenylphosphine, tributylphosphine, tri-tert-butylphosphonium tetrafluoroborate, 1,3-bis(diphenylphosphino)propane, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 1,1'-bis(diphenylphosphino)-ferrocene, 2-(di-tert-butylphosphino)biphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, and the like can be preferably used as the phosphines.

(D) The compound wherein R^{11} is an optionally substituted amino group can be prepared by coupling a compound of the formula (IX) wherein

X^{10} is a halogen atom with a compound of the formula:

$(R^{20})_3Sn\text{-}NR^{21}R^{22}$

wherein R^{20} is an alkyl group and $NR^{21}R^{22}$ is an optionally substituted amino group.

The coupling reaction can be carried out in the presence of a palladium catalyst in the presence or absence of a base in a suitable solvent.

The palladium catalysts, bases, and phosphines referred to in (C) can be used in the same manner as (C) above.

(E) The compound wherein R^{11} is a cyano group can be prepared by cyanating a compound of the formula (IX) wherein X^{10} is a halogen atom.

The cyanation can be carried out by reacting a starting compound with a metal cyanide including sodium cyanide, potassium cyanide, or zinc cyanide in the presence of a palladium catalyst in a suitable solvent.

The same palladium catalyst as that described in (C) can be preferably used.

(F) The compound wherein R^{11} is an optionally substituted alkoxycarbonyl group can be prepared by reacting a compound of the formula (IX) wherein X^{10} is a halogen atom with a corresponding alkylalcohol under carbon monoxide using a palladium catalyst in the presence of a base in a suitable solvent.

The same palladium catalyst and base as those described in (C) can be preferably used.

Additionally, the reaction can be more preferably carried out by adding a ligand, and phosphines referred to in (C) can be preferably used as the ligand.

(G) The compound wherein R^{11} is an optionally substituted alkenyl group can be prepared by coupling a compound of the formula (IX) wherein X^{10} is a halogen atom with a corresponding alkene.

The coupling reaction can be carried out in the presence of a

palladium catalyst in the presence or absence of a base in a suitable solvent.

The same palladium catalyst as that described in (C) can be preferably used.

The same base as referred to in (C) can be preferably used and silver carbonate can also be used.

Additionally, the reaction can be more preferably carried out by adding a ligand, and phosphines referred to in (C) can be preferably used as the ligand.

(H) The compound wherein R^{11} is an alkoxy group having 3 to 10 carbon atoms or a substituted alkoxy group can be prepared by alkoxylating a compound of the formula (IX) wherein X^{10} is a halogen atom.

The alkoxylation can be carried out by optionally adding a copper catalyst to react a starting compound with a corresponding alcohol in a suitable solvent or neat in the presence of a base.

The same base as referred to in (C), in particular, cesium carbonate can be preferably used.

The copper catalyst including copper iodide, copper bromide, copper chloride, copper acetate, copper trifluoromethanesulfonate, and the like can be preferably used.

Additionally, the reaction proceeds more preferably when 1,10-phenanthroline, 2-aminopyridine, or the like is added.

(I) The compound wherein R^{11} is an optionally substituted heterocyclic group can be prepared by coupling a compound of the formula (IX) wherein X^{10} is a halogen atom with a corresponding heterocyclic boronic acids or a corresponding heterocyclic boronic ester.

The coupling can be carried out in the presence of a palladium catalyst, and in the presence or absence of a base in a suitable solvent.

The reaction can be carried out in the same manner as (C).

(J) The compound wherein R^{11} is an alkoxycarbonylalkylsulfonyl

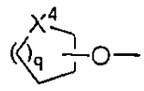
group can be prepared by reacting a compound of the formula (IX) wherein X^{10} is a halogen atom with an alkoxycarbonylalkylsulfinic acid alkaline metal salt.

The alkoxycarbonylalkylsulfinic acid alkaline metal salt can be prepared according to the method described, for example, in Baskin et al., Tetrahedron Lett., 43, 8479 (2002).

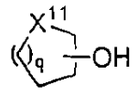
Additionally, the reaction can be carried out in the presence of a copper catalyst in a suitable solvent according to the method described in the said literature.

The same copper catalyst as described in (H) can be used, and in particular, copper iodide can be preferably used.

(K) The compound wherein R^{11} is a group of the formula:



wherein the symbols have the same meaning as defined above can be prepared by condensing a compound wherein R^{11} is a hydroxy group with a compound of the formula:



wherein X^{11} is O, SO, SO_2 or NR^P (R^P is a protecteing group) and q is an integer from 1 to 4, and if needed, removing a protecting group for amino group.

As a protecting group, a conventional protecting group including benzyloxycarbonyl group, tert-butoxycarbonyl group, and the like can be used.

The reaction can be carried out in a suitable solvent in the presence of phosphines and azodicarboxylic esters. The reaction can be carried out in the same manner as the PROCESS 4-(A).

The removal of a protecting group can be carried out in a conventional manner including catalytic reduction, acid-treatment, and the

like, depending on the type of a protecting group.

The reactions (A) to (K) for conversions of R^{11} can also be applied for conversion in the same manner of an other substituent (R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 or R^{10}) as appropriate.

Additionally, a substituent(s) of a compound (I) of the present invention can be converted into different one(s) within the scope of the compound (I) according to the following methods as appropriate.

In the following each process, a conventional base can be used as a base, and unless otherwise specified, the base referred to in the PROCESS 1 can be preferably used.

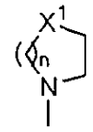
Additionally, in the following each process, a conventional acid can be used as an acid, and unless otherwise specified, a mineral acid including hydrochloric acid, nitric acid, sulfuric acid, or an organic acid represented by sulfonic acids (e.g., methanesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid) or carboxylic acids (e.g., acetic acid, trifluoroacetic acid) can be preferably used.

Further additionally, in the following each process, any solvent which dose not disturb the reaction can be used, and as such, the solvent referred to in the PROCESS 1 can be preferably used.

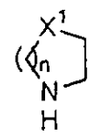
The leaving group includes a halogen atom including chlorine atom, bromine atom, iodine atom, and a substituted sulfonyloxy group including methanesulfonyloxy group, trifluoromethanesulfonyloxy group, and toluenesulfonyloxy group.

In addition, in the following each process, "a saturated or unsaturated monocyclic or bicyclic heterocyclic group having one to four heteroatoms independently selected from oxygen atom, sulfur atom and nitrogen atom" in R^5 is simply referred to as "a heterocyclic group".

(1) The compound wherein R^5 is a heterocyclic group substituted by an optionally substituted amino group or a group of the formula:



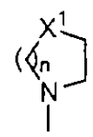
wherein the symbols have the same meaning as defined above can be prepared by reacting a compound (I) wherein R^5 is a heterocyclic group substituted by an optionally substituted alkylsulfonyloxy group with a corresponding amine or a compound of the formula:



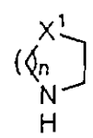
wherein the symbols have the same meaning as defined above in the presence of a palladium catalyst, and in the presence or absence of a base in a suitable solvent or neat.

The reaction can be carried out in the same manner as the PROCESS 4-(C).

(2) The compound wherein R^5 is a heterocyclic group substituted by an optionally substituted amino group or a group of the formula :



wherein the symbols have the same meaning as defined above can also be prepared by reacting a compound wherein R^5 is a heterocyclic group substituted by a halogen atom or an optionally substituted alkylsulfonyloxy group with a corresponding amine or a compound of the formula:



wherein the symbols have the same meaning as defined above.

The reaction can be carried out by optionally adding a copper

catalyst in the presence or absence of a base in a suitable solvent.

Copper iodide, copper bromide, copper chloride, copper acetate, copper trifluoromethanesulfonate, and the like can be preferably used as the copper catalyst.

The same base as referred to in the PROCESS 4-(C) can be preferably used.

Additionally, the reaction proceeds more preferably when N,N'-dimethylethylenediamine, 1,10-phenanthroline, ethylene glycol, phenylphenol, and the like is added.

(3) The compound wherein R^5 is a heterocyclic group substituted by an optionally substituted alkylthio group can be prepared by reacting a compound wherein R^5 is a heterocyclic group substituted by a halogen atom or an optionally substituted alkylsulfonyloxy group with a corresponding alkylthiol.

The reaction can be carried out in the same manner as previously described in the PROCESS 4-(H) and facilitated by adding 1,10-phenanthroline or ethylene glycol.

(4) The compound wherein R^5 is a heterocyclic group substituted by an optionally substituted heterocyclic group can be prepared by coupling a compound wherein R^5 is a heterocyclic group substituted by a halogen atom or an optionally substituted alkylsulfonyloxy group with a corresponding heterocyclic alkyl tin compound.

The reaction can be carried out in the same manner as the PROCESS 4-(D).

(5) The compound wherein R^5 is a heterocyclic group substituted by an alkoxy group or an alkoxyphenylalkoxy group can be prepared by reacting a compound wherein R^5 is a heterocyclic group substituted by an alkylsulfonyl group with a corresponding alkaline metal alkoxide in a suitable solvent. The corresponding alkaline metal alkoxide can be obtained by treating a corresponding alkylalcohol with alkaline metal

hydride or alkaline metal in the said solvent.

(6) The compound having an aminoalkyl group as a substituent on R^5 can be prepared by catalytically reducing a compound having a cyano group or a cyanoalkyl group as a substituent on R^5.

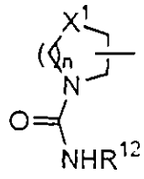
The catalytic reduction can be carried out by using a catalyst under hydrogen in a suitable solvent according to a conventional manner. The catalyst includes a palladium catalyst including palladium-carbon, a nickel catalyst including Raney nickel, a platinum catalyst including platinum-carbon, and the like.

(7) The compound having an optionally substituted mono- or di-alkylsulfamoylaminoalkyl group as a substituent on R^5 can be prepared by reacting a compound having an aminoalkyl group as a substituent on R^5 with a corresponding halogenated mono- or di-alkylsulfamoyl.

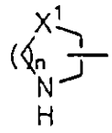
The reaction can be carried out in a suitable solvent in the presence of a base.

(8) The compound having an optionally substituted mono-alkylcarbamoylaminoalkyl group as a substituent on R^5 can be prepared by reacting a compound having an aminoalkyl group as a substituent on R^5 with a corresponding alkyl isocyanate in a suitable solvent.

(9) The compound having a group of the formula:



wherein R^{12} is an alkyl group and the other symbol has the same meaning as defined above as a substituent on R^5 can be prepared by reacting a compound having a group of the formula:



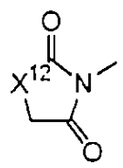
wherein the symbols have the same meaning as defined above as a substituent on R^5 with a corresponding alkyl isocyanate ($R^{12}NCO$). The reaction can be carried out in the same manner as (8).

(10) The compound having an optionally substituted mono- or di-alkylcarbamoylaminoalkyl group as a substituent on R^5 can be prepared by condensing a compound having an aminoalkyl group as a substituent on R^5 with an optionally substituted mono- or di-alkylamine using a carbonylating agent in a suitable solvent in the presence or absence of a base.

A conventional carbonylating agent such as carbonyldiimidazole, phosgene, triphosgene, and the like can be used.

(11) The compound having a morpholinylcarbonylamino group as a substituent on R^5 can be prepared by condensing a compound having an amino group as a substituent on R^5 with morpholine using a carbonylating agent in a suitable solvent. The reaction can be carried out in the same manner as (10).

(12) The compound having a group of the formula:



wherein X^{12} is O or NH as a substituent on R^5 can be prepared by treating a compound having a group of the formula

$H\text{-}X^{12}\text{-}CH_2\text{-}CONH\text{-}$

wherein the symbols have the same meaning as defined above as a substituent on R^5 with a carbonylating agent in a suitable solvent.

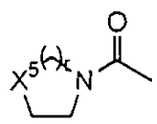
The reaction can be carried out in the same manner as (10).

(13) The compound having an optionally substituted carbamoyl group as a substituent on R^5 can be prepared by condensing a compound having a carboxyl group as a substituent on R^5 with a desirable amine.

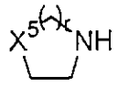
The condensation can be carried out using a condensing agent in a suitable solvent. A conventional condensing agent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, carbonyldiimidazole, and the like can be preferably used.

Additionally, the condensation can be more preferably carried out by adding an activating agent including 1-hydroxybenzotriazole, 1-hydroxysuccinimide, and the like.

(14) The compound having a group of the formula:



wherein the symbols have the same meaning as defined above as a substituent on R^5 can be prepared by condensing a compound having a carboxyl group as a substituent on R^5 with a compound of the formula:



wherein the symbols have the same meaning as defined above.

The reaction can be carried out in the same manner as (13).

(15) The compound having a tetrazolyl group as a substituent on R^5 can be prepared by reacting a compound having a cyano group as a substituent on R^5 with an alkaline metal azide in the presence of an acid in a suitable solvent.

The alkaline metal azide includes sodium azide, lithium azide, and the like.

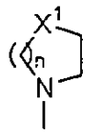
An ammonium salt of a halogenated hydrogen including ammonium chloride can be preferably used as the acid.

(16) The compound having an optionally substituted alkyl tetrazolyl group as a substituent on R^5 can be prepared by alkylating a compound having a tetrazolyl group as a substituent on R^5.

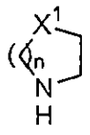
The alkylation can be carried out in the same manner as the

PROCESS 4-(A).

(17) The compound having an optionally substituted amino group or a group of the formula:



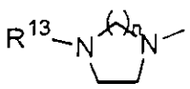
wherein the symbols have the same meaning as defined above as a substituent on R^5 can be prepared by reacting a compound having a halogen atom or an optionally substituted alkylsulfonyloxy group as a substituent on R^5 with a corresponding amine or a compound of the formula:



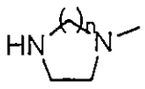
wherein the symbols have the same meaning as defined above.

The reaction can be preferably carried out in the presence or absence of a base in a suitable solvent.

(18) The compound having an optionally substituted alkylamino group or a group of the formula:



wherein R^{13} is an alkyl group optionally substituted by a hydroxy group, an alkoxycarbonyl group, a morpholinyl group or a phenyl group, and n has the same meaning as defined above as a substituent on R^5 can be obtained by reacting a compound having an amino group or a group of the formula:

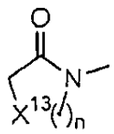


wherein the symbols have the same meaning as defined above as a substituent on R^5 with a corresponding alkyl halide or a corresponding sulfonic alkyl ester.

The sulfonic alkyl ester including methanesulfonic ester, toluenesulfonic ester, trifluoromethanesulfonic ester, and the like can be preferably used.

The reaction can be preferably carried out in the presence or absence of a base in a suitable solvent.

(19) The compound having a group of the formula:



wherein X^{13} is O or NH, and the other symbols have the same meaning as defined above as a substituent on R^5 can be prepared by ring-closing a compound having a group of the formula:

Z^3-$(CH_2)_n$-X^{13}-CH_2-CONH-

wherein Z^3 is a leaving group and the other symbols have the same meaning as defined above as a substituent on R^5.

The reaction can be preferably carried out in the presence or absence of a base in a suitable solvent.

(20) The compound having a carboxyl group as a substituent on R^5 can be prepared by hydrolyzing a compound having an alkoxycarbonyl group as a substituent on R^5.

The hydrolysis can be carried out by treating a starting compound with a base or an acid in a suitable solvent according to a conventional manner. An alkaline metal hydroxide can be preferably used as the base.

(21) The compound containing a carboxyl group as a substituent on R^5 can be prepared by hydrolyzing a compound containing a cyano group as a substituent on R^5.

The hydrolysis can be carried out by treating a starting compound with an acid in a suitable solvent.

(22) The compound containing a carbamoyl group as a substituent on R^5 can be prepared by hydrolyzing a compound containing a cyano

group as a substituent on R^5.

The hydrolysis can be carried out by treating a starting compound with an acid in a suitable solvent.

(23) The compound having a carboxyalkyl group as a substituent on R^5 can also be prepared by catalytically reducing a compound having a carboxyalkenyl group, a benzyloxycarbonylalkenyl group or a benzyloxycarbonylalkyl group as a substituent on R^5.

The catalytic reduction can be carried out in the same manner as (6).

(24) The compound having a hydroxy group as a substituent on R^5 can be prepared by hydrolyzing a compound wherein R^5 has an alkanoyloxy group.

The hydrolysis can be carried out in the same manner as (20).

(25) The compound containing sulfin (SO) or sulfoxide (SO_2) in a substituent on R^5 can be prepared by oxidizing a compound having S in a substituent on R^5 (e.g., a compound having a thiomorpholinyl group or an alkylthioalkyl group as a substituent on R^5).

The oxidation can be carried out by treating a starting compound with an oxidizing agent in a suitable solvent.

Peroxides such as hydrogen peroxide, m-chloroperbenzoic acid, acetyl hydroperoxide, and the like can be preferably used as the oxidizing agent.

(26) The compound containing N-oxide in a substituent on R^5 can be prepared by oxidizing a compound having N in a substituent on R^5 (e.g., a compound having a pyridyl group as a substituent on R^5).

The oxidation can be carried out in the same manner as (25).

(27) The compound having a 1,2-dihydroxyalkyl group as a substituent on R^5 can be prepared by treating a compound having an alkyl group substituted by mono- or di-alkyldioxolanyl group as a substituent on R^5 with an acid in a suitable solvent.

A strongly acidic resin can also be preferably used as the acid, in

addition to those previously described.

(28) The compound having an alkyl group substituted by a hydoxy group and an optionally substituted alkoxy group as substituents on R^5 can be prepared by reacting a compound having an oxylanylalkyl group as a substituent on R^5 with an alkaline metal salt of the corresponding alcohol in a suitable solvent.

The alkaline metal salt of alcohol includes a lithium salt, a sodium salt, a potassium salt, and the like.

(29) The compound having an alkyl group substituted by a hydoxy group and an amino group, or an alkyl group substituted by a hydroxy group and an optionally substituted mono- or di-alkylamino group as substituents on R^5 can be prepared by reacting a compound having an oxylanylalkyl group as a substituent on R^5 with ammonia or a corresponding mono- or di-alkylamines in a suitable solvent.

(30) The compound having a hydroxycarbamimidoyl group as a substituent on R^5 can be prepared by reacting a compound having a cyano group as a substituent on R^5 with hydroxylamine or a salt thereof in a suitable solvent. This process can be carried out in the same manner as the PROCESS 2-(b) previously described.

(31) The compound having an oxodihydrooxadiazolyl group as a substituent on R^5 can be prepared by reacting a compound having a hydroxycarbamimidoyl group as a substituent on R^5 with a carbonylating agent in a suitable solvent in the presence or absence of a base.

The same carbonylating agent as that described in (10) can be used.

(32) The compound having a sulfo group as a substituent on R^5 can be prepared by hydrolyzing a compound having an alkoxycarbonylalkylsulfonyl group as a substituent on R^5.

The hydrolysis can be carried out in the same manner as (20).

(33) The compound having a sulfamoyl group as a substituent on R^5 can be prepared by condensing a compound having a sulfo group as a

substituent on R^5 with a desirable amine.

The condensation can be carried out by treating a compound having a sulfo group as a substituent on R^5 with a halogenating agent in a suitable solvent, followed by reacting the resulting compound with a desirable amine in the presence or absence of a base.

A conventional halogenating agent including thionyl halide, phosphorus oxyhalide, or the like can be used.

(34) The compound having a hydroxyalkyl group as a substituent on R^5 can be prepared by reducing a compound having a carboxyalkyl group as a substituent on R^5, or by converting the carboxyl group into an acid anhydride or an ester and reducing the resulting compound.

A process for conversion into an acid anhydride can be carried out by reacting a starting compound with a halogenated alkyl formate in a suitable solvent in the presence of a base.

A process for conversion into an ester can be carried out by reacting a starting compound with an alcohol in the presence of a condensing agent in a suitable solvent. This process can be carried out in the same manner as (33) except that a desirable alcohol is used in place of amine.

The reduction can be carried out by treating the resulting compound with a reducing agent in a suitable solvent.

Boron hydrides (sodium borohydride, and the like), aluminum hydrides (lithium aluminum hydride, diisobutylaluminum hydride, and the like) can be preferably used as the reducing agent.

(35) The compound wherein R^{10} is an aromatic group substituted by a cyano group, optionally having one to three heteroatoms independently selected from oxygen atom, sulfur atom and nitrogen atom (hereinafter ,referred to as "an aromatic group"), can be prepared by cyanating a compound wherein R^{10} is an aromatic group substituted by a halogen atom.

The cyanation can be carried out in the same manner as the

PROCESS 4-(E).

(36) The compound wherein R^1 is a hydrogen atom can be prepared by acid-treatment or reduction of a compound wherein R^1 is a tert-butoxycarbonyl group or a benzyloxycarbonyl group.

The acid-treatment can be carried out in the same manner as (27) and the reduction can be carried out in the same manner as (23).

(37) The compound wherein R^1 is an optionally substituted alkoxycarbonyl group, or an optionally substituted carbamoyl group can be prepared by reacting a compound wherein R^1 is a hydrogen atom with a carbonylating agent, or a desirable alcohol or a desirable amine in a suitable solvent.

The reaction can be carried out in the same manner as (10).

(38) The compound having an amino group as a substituent on R^5 can be prepared by reacting a compound having a carboxyl group as a substituent on R^5 under Curtius rearrangement reaction condition

Curtius rearrangement reaction can be carried out using a conventional azidating agent (e.g., diphenylphosphorylazide) in a suitable solvent in the presence of a base.

The reaction may also be carried out by adding an alcohol to provide a compound having an optionally substituted alkoxycarbonylamino group as a substituent on R^5, followed by removing the alkoxycarbonyl group.

The removal of the alkoxycarbonyl group can be carried out in a conventional manner such as an acid-treatment or a reduction depending on the type of alkoxycarbonyl group to be removed. The acid-treatment can be carried out in the same manner as (27) and the reduction can be carried out in the same manner as (23).

(39) The compound having a hydroxy group as a substituent on R^5 can be prepared by catalytically reducing a compound having a benzyloxy group as a substituent on R^5. The reduction can be carried out in the same manner as (23).

(40) The compound having an oxo group as a substituent on R^5 can be prepared by oxidizing a compound having a hydroxy group as a substituent on R^5.

The oxidation can be carried out by using an oxidizing agent in a suitable solvent.

A conventional oxidizing agent can be used as the oxidizing agent, such as chromate-pyridine complex, pyridinium chlorochromate, pyridinium dichromate, Dess-Martin reagent (1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one), dimethylsulfoxide, and the like

(41) The compound containing an optionally substituted alkoxy group as a substituent on R^5 can be prepared by alkylating a compound containing a hydroxy group as a substituent on R^5.

The alkylation can be carried out by using a corresponding compound in the same manner as the PROCESS 4-(A).

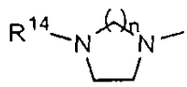
(42) The compound having an optionally substituted alkanoylamino group as a substituent on R^5 can be prepared by condensing a compound having an amino group as a substituent on R^5 with a corresponding carboxylic acid or a reactive derivative thereof.

The condensation with the corresponding carboxylic acid can be preferably carried out in a suitable solvent in the presence of a condensing agent. The reaction can be carried out in the same manner as (13).

Additionally, the condensation with the reactive derivative of the corresponding carboxylic acid can be carried out in a suitable solvent or neat in the presence or absence of a base.

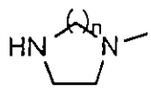
The reactive derivative includes an acid halide, an acid anhydride, an activated ester, an activated amide, and the like.

(43) The compound having a group of the formula:



wherein R^{14} is an alkanoyl group optionally substituted by a hydroxy group

or an alkoxy group, and n has the same meaning as defined above as a substituent on R^5 can be prepared by condensing a compound of a group of the formula:



wherein the symbols have the same meaning as defined above as a substituent on R^5 with a corresponding carboxylic acid or a reactive derivative thereof.

The reaction can be carried out in the same manner as (42).

(44) The compound having a maleimide group as a substituent on R^5 can be prepared by reacting a compound having an amino group as a substituent on R^5 with a maleic anhydride. The reaction can be carried out in a suitable solvent.

(45) The compound having an alkyl group substituted by a pyridyl group and a hydroxy group as substituents on R^5 can be prepared by reacting a compound having an alkyl group substituted by a pyridyl group of which nitrogen atom is oxidized as a substituent on R^5 with a trifluoroacetic anhydride. The reaction can be carried out in a suitable solvent.

(46) The compound having a halogen atom as a substituent on R^5 can be prepared by treating a compound having a hydroxy group as a substituent on R^5 with a halogenating agent.

As the halogenating agent, a conventional halogenating agent including thionyl chloride, phosphorus oxychloride, as well as carbon tetrahalide (e.g., carbon tetrachloride, carbon tetrabromide, and the like) and phosphines (e.g., triphenylphosphine, tritolylphosphine, triethylphosphine, and the like) can be preferably used.

(47) The compound having a cyanoalkyl group as a substituent on R^5 can be prepared by reducing a compound having a cyanoalkenyl group as a substituent on R^5.

The reduction can be carried out by treating a starting compound with a reducing agent or by catalytically reducing in a suitable solvent.

Any reducing agent can be used subject that it reduces only a double bond without affecting a cyano group. For example, sodium bis(2-methoxyethoxy)aluminum hydride in the presence of a copper bromide can be preferably used.

The catalytic reduction can be carried out in the same manner as (23).

(48) The compound having a hydroxyalkyl group as a substituent on R^5 can be prepared by reducing a compound having a formyl group as a substituent on R^5.

The reduction can be carried out by treating a starting compound with a reducing agent in a suitable solvent.

The reaction can be carried out in the same manner as the process for reducing in (34).

(49) The compound wherein R^7 is a hydroxy group can be prepared by demethylating a compound wherein R^7 is a methoxy group.

The demethylation can be carried out by treating a starting compound with a demethylating agent in a suitable solvent.

A conventional agent including trimethylsilyl iodide, hydrogen bromide/acetic acid, boron tribromide, concentrated sulfuric acid, and the like can be used as the demethylating agent.

(50) The compound wherein R^7 is an optionally substituted alkoxy group can be prepared by alkylating a compound wherein R^7 is a hydroxy group.

The alkylation can be carried out in the same manner as the PROCESS 4-(A).

(51) The compound wherein R^7 is an optionally substituted alkylsulfonyloxy group can be prepared by alkylsulfonylating a compound wherein R^7 is a hydroxy group.

The alkylsulfonylation can be carried out by reacting a corresponding alkylsulfonyl halide or a corresponding alkylsulfonic anhydride in a suitable solvent in the presence or absence of a base.

(52) The compound wherein R^7 is a cyano group can be prepared by cyanating a compound wherein R^7 is an optionally substituted alkylsulfonyloxy group.

The cyanation can be carried out in the same manner as the PROCESS 4-(E).

(53) The compound wherein R^7 is an aminoalkyl group can be prepared by reducing a compound wherein R^7 is a cyano group.

The reduction can be carried out in the same manner as (6).

(54) The compound wherein R^7 is an alkyl group can be prepared by alkylating a compound wherein R^7 is an optionally substituted alkylsulfonyloxy group.

The alkylation can be carried out by reacting alkyl aluminums in the presence of a palladium catalyst, a silver catalyst and a copper catalyst in a suitable solvent.

Tetrakis(triphenylphosphine)palladium as the palladium catalyst, silver carbonate as the silver catalyst, copper (I) chloride as the copper catalyst can be preferably used.

(55) The compound having an imidazolinyl group or an oxazolinyl group as a substituent on R^5 can be prepared by (i) reacting a compound containing a cyano group as a substituent on R^5 with a desirable alcohol in the presence of an acid in a suitable solvent or neat to provide a compound containing an alkoxycarbonimidoyl group as a substituent on R^5, and (ii) reacting the compound containing an alkoxycarbonimidoyl group as a substituent on R^5 with 2-aminoethanol or ethylene diamine in a suitable solvent or neat.

(56) The compound having a carboxyl group as a substituent on R^1 can be prepared by (i) oxidizing a compound containing a hydroxyalkyl

group as a substituent on R^1 in the same manner as (40) to provide a compound containing an oxo group as a substituent on R^1, and (ii) oxidizing the compound containing an oxo group as a substituent on R^1.

The oxidization for the second step can be carried out by using an oxidizing agent in a suitable solvent. Sodium chlorite, Silver(I) oxide, Sodium periodate and the like can be preferably used as the oxidizing agent.

(57) The compound having a carboxyl group as a substituent on R^1 can be directly prepared by oxidizing a compound containing a hydroxyalkyl group as a substituent on R^1.

The oxidization can be carried out by using Jones reagent, potassium permanganate, and the like as the oxidizing agent.

(58) The compound wherein R^1 is hydrogen atom can be prepared by treating a compound wherein R^1 is ethoxycarbonyl group with a silyl halides or a base. Trimethylsilyl iodide can be preferably used as the silyl halides. Sodium hydroxide can be preferably used as the base.

In each process for preparing a compound of the formula (I) described above, when protection of a functional group contained in any compound is needed, the protection can be carried out in a conventional manner ad libitum. General statement related to protecting groups and their use is provided by Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, New York, 1991.

When an amino group is protected by a benzyloxycarbonyl group, the protecting group can be removed by a catalytic reduction under hydrogen in a suitable solvent.

When a hydroxy group is protected by a benzyl group, the protecting group can also be removed by a catalytic reduction in a similar manner as above.

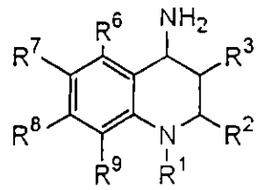
When an amino group is protected by a t-butoxycarbonyl group, the protecting group can be removed by treating a starting compound with an

acid (e.g., hydrochloric acid, trifluoroacetic acid, toluenesulfonic acid, and the like) in a suitable solvent.

When a hydroxy group is protected by a tetrahydropyranyl group, the protecting group can also be removed by treating a starting compound with an acid in a similar manner as above.

The reactions (1) to (58) for canversion of R^1, R^5, R^7 or R^{10} can also be applied for conversion in the same manner of an other substituent of the present compouind (I) as appropriate.

The starting compound (II) is a novel compound, and can be prepared by condensing a compound of the formula (X):



(X)

wherein the symbols have the same meaning as defined above with a compound of the formula (XI):

R^5-Z^4 (XI)

wherein Z^4 is a leaving group and R^5 has the same meaning as defined above.

As the leaving group, a halogen atom including chlorine atom, bromine atom, iodine atom, and a substituted sulfonyloxy group including methanesulfonyloxy group, p-toluenesulfonyloxy group, trifluoromethanesulfonyloxy group are preferably used.

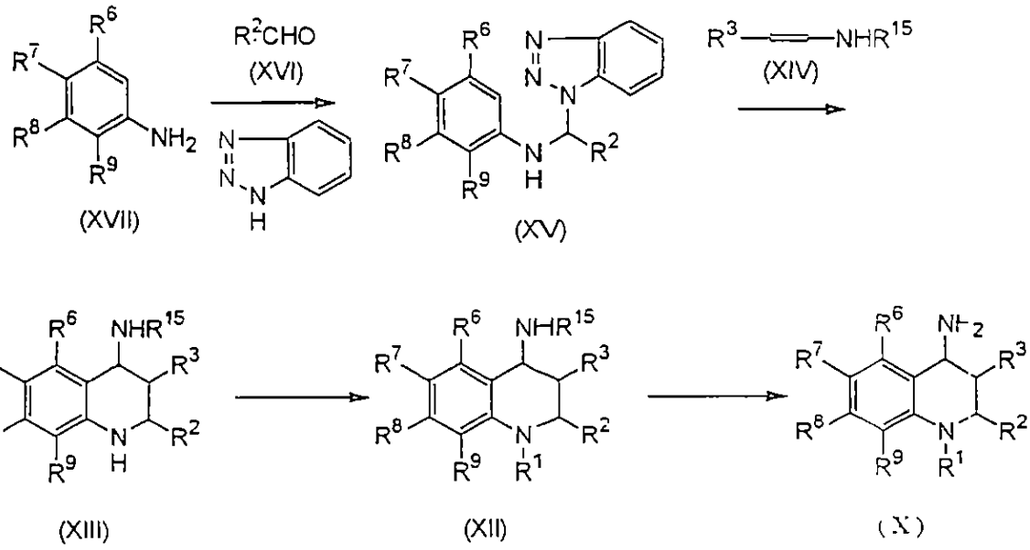
The reaction can be carried out in a suitable solvent (e.g., 1,4-dioxane, dimethylformamide, 1,3-dimethylimidazolidinone, and the like) in the presence or absence of a base (e.g., diisopropylethylamine, and the like) from room temperature to under heating.

The reaction can also be carried out by adding a palladium catalyst (e.g., tris(dibenzylidenacetone)dipalladium) and a phosphine [for example, triphenylphosphine, tributylphosphine, or 2-(di-tert-butyl-

phosphino)biphenyl] at room temperature in the presence of a base (e.g., sodium tert-butoxide), if desired.

A compound of the formula (X) can be prepared according to the method described in WO00/17165 or US 6313142.

Alternatively, the compound (X) can be prepared according to the following scheme:



wherein R^{15} is a protecting group for amino group and the other symbols have the same meaning as defined as above.

A conventional protecting group including a benzyloxycarbonyl group can be used as the protecting group for amino group. Additionally, an optically-active compound (X) can be prepared by protecting amino group with an optically-active protecting group for amino group (e.g., an optically-active α-substituted benzyloxycarbonyl group having a chiral center at the benzyl position, such as α-methylbenzyloxycarbonyl group), resolving diastereomers in the process for preparation of compound (XII) or compound (XIII), and removing the protecting group.

A compound of the formula (XV) can be prepared by reacting benzotriazole, a compound of the formula (XVI) and a compound of the formula (XVII) in a suitable solvent (e.g., toluene) at room temperature.

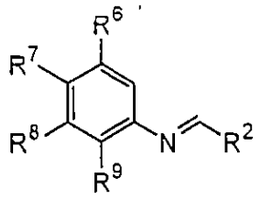
A compound of the formula (XIII) can be prepared by reacting a compound of the formula (XIV) with a compound of the formula (XV) in the presence of an acidic catalyst (e.g., an organic acid including p-toluenesulfonic acid, acetic acid, methanesulfonic acid, or Lewis acid including boron trifluoride-diethylether complex, titanium tetrachloride, aluminum chloride) in a suitable solvent (e.g., toluene, tetrahydrofuran, methylene chloride, and the like) under heating or at room temperature (e.g., 0°C to 150°C, preferably 25°C to 120°C).

A compound of the formula (XII) can be prepared by alkanoylation, alkoxycarbonylation, alkylation, and the like of a compound of the formula (XIII) as appropriate.

A compound of the formula (X) can be prepared by removing a protecting group for amino group of a compound of the formula (XII). The removal of the protecting group can be carried out in a conventional manner including acid-treatment, base-treatment, reduction, and the like depending on the type of the protecting group. When a benzyloxycarbonyl group or an α-substituted benzyloxycarbonyl group is used, they can be removed by a catalytic reduction in a suitable solvent (e.g., ethanol, methanol, tetrahydrofuran, acetic acid, and the like) under hydrogen. The removal of a protecting group for amino group of a compound of the formula (XIII) can be carried out in the same manner as the removal of the protecting group for amino group of a compound of the formula (XII).

When an optically-active protecting group such as α-substituted benzyloxycarbonyl group is used as a protecting group for amino group, resolution of a diastereomer can be carried out in a conventional manner such as recrystallization or column chromatography.

A compound of the formula (XIII) can also be prepared by reacting a compound of the formula (XIV) with a compound of the formula (XVIII).



(XVIII)

This reaction can be carried out in the same manner as the reaction of a compound of the formula (XIV) with a compound of the formula (XV).

Additionally, respective substituents R^1, R^5, R^6, R^7, R^8 and R^9 can be converted into a desirable substituent in accordance with any one of processes from the PROCESS 4-(A) to (K) and from (1) to (55).

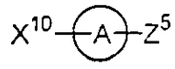
A compound of the formula (IV) can be prepared by condensing a compound of the formula (X) with a compound of the formula (III)

R^{10}-R^4-Z^1 (III)

wherein the symbols have the same meaning as defined above.

The condensation can be carried out in the same manner as described in WO00/17165 or the PROCESS 1 above.

A compound of the formula (IX) can be prepared by condensing a compound of the formula (IV) with a compound of the formula:



wherein Z^5 is a leaving group and the other symbols have the same meaning as defined above.

As the leaving group, a halogen atom including chlorine atom, bromine atom, iodine atom; a substituted sulfonyloxy group including methanesulfonyloxy group, p-toluenesulfonyloxy group, trifluoromethanesulfonyloxy group can be preferably used.

The condensation can be carried out in the same manner as the one of the said compound (X) with the compound (XI).

Additionally, the compound of the formula (IX) wherein Ring A is a tetrazolyl group and X^{10} is a hydrogen atom can be prepared by reacting a compound of the formula (V) with an alkyl metal azide. The reaction can

be carried out in the same manner as (15) described above.

Further, the compound of the formula (IX) wherein X^{10} is a hydroxyl group can be prepared by (i) reacting a compound wherein X^{10} is a halogen atom with diboron or borane to provide a compound wherein X^{10} is a boronic esters, and (ii) reacting the compound wherein X^{10} is a boronic esters with peroxides.

Hydrogen peroxide solution, m-chloroperbenzoic acid or OXONE™ (Manufactured by DuPont) can be preferably used as the peroxides.

Many of starting materials and reagents for preparation of the aforementioned compound of the formula I are either commercially available or disclosed in literatures, or can be readily prepared by a method that is disclosed in literatures or used generally in the organic synthesis.

As used herein, "3,4-dihydro-2H-quinoline" represents the same structure as "1,2,3,4-tetrahydroquinoline".

Experiment

The inhibitory activity of the compounds of the present invention against CETP was tested in this experiment.

Preparation of Acceptor Microemulsion

A solution of 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (3.5 mg), cholesteryl oleate (3mg) and triolein (0.7 mg) in chloroform was mixed and lipid was air-dried under nitrogen gas to remove solvent. 1,4-Dioxane (0.25 ml) was then added and the mixture was stirred for dissolution. The resultant lipid solution (0.2 ml) was slowly injected under the surface of Tris-saline-EDTA(TSE) buffer solution [10mM Tris/HCl (pH 7.4), 0.15M NaCl, 2mM EDTA] (10 ml) with Hamilton syringe, while sonicating in ice-bath. After 1-hour-sonication in ice-bath, the solution was stored at 4 °C.

Preparation of Donor Microemulsion

A solution of egg PC (phosphatidylcholine) (0.33 mg) and BODIPY-CE (0.62 mg) in chloroform was mixed. After removing solvent by air-drying lipid under nitrogen gas, TSE buffer solution (3 ml) was added and the

solution was sonicated in ice-bath. This solution was filtered to sterilize through 0.22 μm filter and stored at 4 °C.

Inhibitory Activity against CETP in vitro

A test solution was prepared using dimethyl sulfoxide as a solvent. Plasma from a healthy volunteer was diluted to 0.64 % with TSE buffer, and to the resultant plasma solution (187 μl) was added a test solution (3 μl) or the solvent alone followed by incubation at 37 °C for 24 hours. After addition of TSE buffer solution (10 μL) containing 5 % donor micro-emulsion and 5 % acceptor microemulsion, the mixture was incubated at 37 °C for 3 hours. Before and after the incubation, the fluorescence intensity was measured at Ex.550nm/Em.600nm. CETP activity was defined as the difference between the measurements obtained before incubation and after incubation. The decreasing rate of the difference in the sample was defined as the inhibition rate of CETP activity. IC_{50} for each sample was calculated from the inhibition rate of CETP activity.

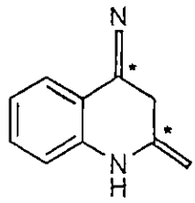
Results

Example No.	IC_{50} (nM)
1	0.17
16	4.2
127	0.89
174	0.23
198	0.66
231	0.53
275	0.18

EXAMPLES

The present invention is illustrated in more detail by Examples and Reference Examples, but the present invention should not be construed to be limited thereto.

In Examples, the compounds having a structure of the formula:



indicate that the configuration thereof is (2R*,4S*). Besides, Me means a methyl group.

Example 1

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3 g) and 5-bromo-2-chloropyrimidine (3.7 g) are dissolved in N,N-dimethylformamide (30 ml), and the mixture is stirred at 150°C for 5 hours. The reaction solution is cooled to room temperature, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 8:1→4:1) to give (2R,4S)-4-(5-bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.2 g). MS (m/z): 473/475 $[M+H]^+$

(2) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.2 g) is dissolved in N,N-dimethylformamide (20 ml), and thereto is added sodium hydride (62.7 %, 223 mg) under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. To the mixture is added 3,5-bis(trifluoromethyl)benzyl bromide (1.3 ml) under ice-cooling, and the mixture is stirred at room temperature for one hour. A saturated brine and ethyl acetate are added to the mixture, and the organic layer is dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 10:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromo-

pyrimidin-2-yl}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.75 g). MS (m/z): 699/701 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (94 mg), tris(dibenzylideneacetone)dipalladium (2.5 mg) sodium tert-butoxide (19 mg), 2-(di-tert-butylphosphino)biphenyl (3 mg), morpholine (18 µl) are dissolved in toluene (1 ml), and the mixture is stirred at room temperature under nitrogen atmosphere for 60 hours. To the reaction solution is added acetic acid, and thereto are added water and ethyl acetate. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 19:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (40 mg). MS (m/z): 706 $[M+H]^+$

Examples 2-6

The corresponding starting compounds are treated in a similar manner to Example 1-(3) to give the compounds as listed in Table 1.

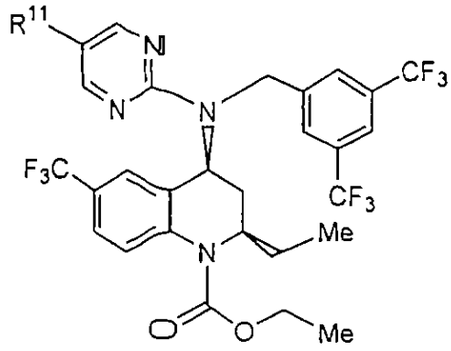
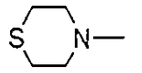
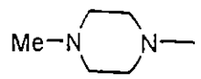
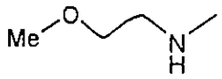
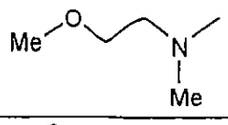
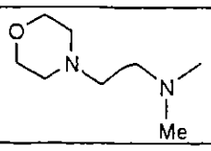


Table 1

Example	R^{11}	Physical properties, etc.
2		MS (m/z): 722 $[M+H]^+$

3		MS (m/z): 719 $[M+H]^+$
4		MS (m/z): 694 $[M+H]^+$
5		MS (m/z): 708 $[M+H]^+$
6		MS (m/z): 763 $[M+H]^+$

Example 7

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(thiomorpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (75 mg) is dissolved in chloroform (3 ml), and thereto is added m-chloroperbenzoic acid (25 mg), and the mixture is stirred at room temperature overnight. To the reaction solution are added water and chloroform, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; chloroform:acetone = 10:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(1-oxothiomorpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (34 mg). MS (m/z): 738 $[M+H]^+$

Example 8

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (250 mg) and dichlorobis(tri-o-tolylphosphine)palladium (5.9 mg) are dissolved in toluene (2 ml), and the mixture is heated at 100°C under nitrogen atmosphere. To the reaction solution is added (dimethylamino)trimethyltin (118 mg), and the mixture is stirred for 2 hours. The

mixture is allowed to cool to room temperature, and the reaction solution is concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 5:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (18 mg). MS (m/z): 664 $[M+H]^+$

Example 9

(1) (2R,4S)-4-Amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (600 mg) and 2-chloro-5-propylpyrimidine (1.5 g) are dissolved in 1,3-dimethylimidazolidinone (10 ml), and the mixture is stirred at 135°C for 72 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 6:1→4:1) to give (2R,4S)-2-ethyl-4-(5-propylpyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (250 mg). MS (m/z): 437 $[M+H]^+$

(2) (2R,4S)-2-Ethyl-4-(5-propylpyrimidin-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (240 mg) and 3,5-bis(trifluoromethyl)benzyl bromide (337 mg) are dissolved in N,N-dimethylformamide (3 ml), and thereto is added sodium hydride (62.7 %, 32 mg) at room temperature, and the mixture is stirred at the same temperature for 2 hours. To the reaction solution is added acetic acid, and water and ethyl acetate are added thereto. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 49:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-propylpyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (130 mg). MS (m/z): 663 $[M+H]^+$

Example 10

To (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1 g) are added N,N-dimethylformamide (10 ml), tetrakis-(triphenylphosphine)palladium (a catalytic amount), and zinc cyanide (176 mg), and the mixture is stirred at 110°C under nitrogen atmosphere for 4 hours. The reaction solution is cooled to room temperature, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 10:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-cyanopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (760 mg). MS (m/z): 646 $[M+H]^+$

Example 11

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-cyanopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in ethanol (3 ml), and thereto is added a catalytic amount of Raney nickel, and the mixture is stirred at room temperature overnight under hydrogen atmosphere. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 1:1) to give (2R,4S)-4-{(5-aminomethylpyrimidin-2-yl)-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (142 mg). MS (m/z): 650 $[M+H]^+$

Example 12

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-aminomethyl-pyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-

1-carboxylic acid ethyl ester (92 mg) and an excess amount of triethylamine are dissolved in methylene chloride (2 ml), and thereto is added an excess amount of N,N-dimethylsulfamoyl chloride under ice-cooling. The mixture is stirred at room temperature for 2 hours, and to the reaction solution are added a saturated brine and ethyl acetate. The organic layer is dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→67:33) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(N,N-dimethylsulfamoyl)aminomethylpyrimidin-2-yl]}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (54 mg). MS (m/z): 757 $[M+H]^+$

Example 13

Acetic acid (88 µl) is dissolved in toluene (3 ml), and thereto are added triethylamine (236 µl) and diphenylphosphoryl azide (466 µl). The mixture is stirred at 70 °C for 1.5 hour. To the reaction solution is added (2R,4S)-4-{(5-aminomethylpyrimidin-2-yl)-[3,5-bis(trifluoromethyl)-benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg), and the mixture is stirred at the same temperature for 4 hours. The mixture is allowed to cool to room temperature, and to the reaction solution are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 1:2) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[(3-methylureido)methyl]-pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (63 mg). MS (m/z): 707 $[M+H]^+$

Example 14

4-(2-Aminoethyl)morpholine (100 mg) is dissolved in tetrahydrofuran (3 ml), and thereto is added N,N'-carbonyldiimidazole (125 mg), and the

mixture is stirred at 70°C for one hour. To the reaction solution is added (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-aminomethylpyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg), and the mixture is stirred at the same temperature for 4 hours. The mixture is allowed to cool to room temperature, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; ethyl acetate) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-[3-(2-morpholin-4-ylethyl)ureidomethyl]pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (118 mg). MS (m/z): 806 [M+H]+

Example 15

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg), palladium acetate (12 mg), 1,1'-bis(diphenylphosphino)ferrocene (55 mg), benzyl alcohol (970 mg) and triethylamine (625 µl) are dissolved in N,N-dimethylformamide (1 ml), and the mixture is stirred at room temperature under carbon monoxide atmosphere for 3 minutes. Subsequently, the mixture is heated at 90°C and stirred overnight. The reaction solution is cooled to at room temperature, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 24:1→3:1) to give (2R,4S)-4-{(5-benzyloxycarbonylpyrimidin-2-yl)-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (250 mg). MS (m/z): 755 [M+H]+

Example 16

(2R,4S)-4-{(5-Benzyloxycarbonylpyrimidin-2-yl)-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (220 mg) is dissolved in a mixture of methanol (2 ml) and tetrahydrofuran (6 ml), and thereto is added 10 % palladium-carbon (100 mg), and the mixture is stirred at room temperature under hydrogen atmosphere for 30 minutes. The catalyst (10 % palladium-carbon) is removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; ethyl acetate) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-(5-carboxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (178 mg). MS (m/z): 665 $[M+H]^+$

Example 17

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-carboxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) and an excess amount of 1-hydroxybenzotriazole hydrate are dissolved in N,N-dimethylformamide (5 ml), and thereto is added an excess amount of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and the mixture is stirred at room temperature for 10 minutes. To the reaction solution are added glycine tert-butyl ester hydrochloride (50 mg) and an excess amount of triethylamine, and the mixture is stirred at room temperature for 10 minutes. To the reaction solution are added an aqueous citric acid solution and ethyl acetate, and the organic layer is washed with a saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9: 1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-tert-butoxycarbonylmethylcarbamoyl-pyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-

1-carboxylic acid ethyl ester. Then, to the mixture is added a 4N hydrochloric acid in 1,4-dioxane (2 ml) at room temperature, and the mixture is stirred overnight. The reaction solution is concentrated under reduced pressure, and the concentrated residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 1:1→chloroform:methanol = 19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-carboxymethylcarbamoylpyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (13 mg). MS (m/z): 722 $[M+H]^+$

Example 18

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg), acrylic acid benzyl ester (125 mg), tris(dibenzylideneacetone)dipalladium (12 mg), diisopropylethylamine (90 µl), tri-tert-butylphosphonium tetrafluoroborate (7.5 mg) are dissolved in 1,4-dioxane (3.5 ml), and the mixture is stirred under nitrogen atmosphere at room temperature for 3 days. To the reaction solution are added an aqueous citric acid solution and ethyl acetate, and the organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 97:3→13:7) to give (2R,4S)-4-{[5-(2-benzyloxycarbonylvinyl)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (186 mg). MS (m/z): 781 $[M+H]^+$

(2) (2R,4S)-4-{[5-(2-Benzyloxycarbonylvinyl)pyrimidin-2-yl]-[3,5-bis-(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (180 mg) is dissolved in a mixture of methanol (5 ml) and tetrahydrofuran (10 ml), and thereto is added 10 % palladium-carbon (300 mg). The mixture is stirred at room temperature under hydrogen atmosphere for 3 hours. The catalyst is removed by

filtration, and the filtrate is concentrated under reduced pressure to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-carboxyethyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (40 mg) MS (m/z): 693 $[M+H]^+$

Example 19

(2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-cyanopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (880 mg), sodium azide (886 mg) and ammonium chloride (729 mg) are dissolved in N,N-dimethylformamide (5 ml), and the mixture is stirred at 100°C for 4 hours. The mixture is allowed to cool to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(tetrazol-5-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (920 mg). MS (m/z): 689 $[M+H]^+$

Example 20

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(tetrazol-5-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (150 mg), potassium carbonate (60 mg), and an excess amount of methyl iodide are dissolved in N,N-dimethylformamide (2 ml), and the mixture is stirred at 50°C for 4 hours. The mixture is allowed to cool to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis (trifluoromethyl)benzyl]-[5-(2-methyl-2H-tetrazol-5-yl)pyrimidin-2-yl]}amino−2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (107 mg). MS (m/z): 703 $[M+H]^+$

Examples 21-22

The corresponding starting compounds are treated in a similar manner to Example 20 to give the compounds as listed in Table 2.

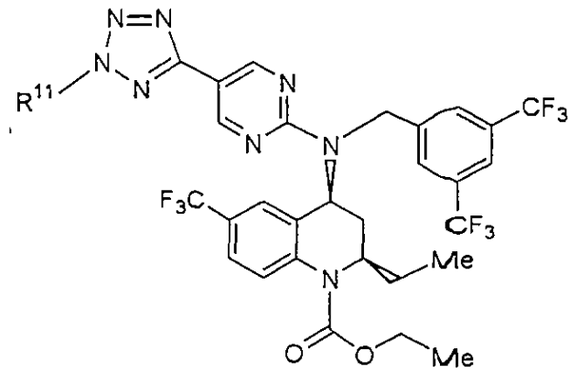
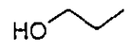
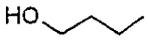


Table 2

Example	R^{11}	Physical properties, etc.
21		MS (m/z): 733 $[M+H]^+$
22		MS (m/z): 747 $[M+H]^+$

Example 23

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(tetrazol-5-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (127 mg), 4-(2-hydroxyethyl)morpholine (35 µl), and triphenylphosphine (76 mg) are dissolved in tetrahydrofuran (3 ml), and thereto is added dropwise 40 % solution of azodicarboxylic acid diethyl ester in toluene (113 µl) under ice-cooling, and the mixture is stirred at room temperature for 4 hours. To the reaction solution are added water and ethyl acetate, and the organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel;

hexane:ethyl acetate = 9:1→67:33) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{5-[2-(2-morpholin-4-ylethyl)-2H-tetrazol-5-yl]pyrimidin-2-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (136 mg). MS (m/z): 802 $[M+H]^+$

Example 24

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.00 g) is dissolved in 1,4-dioxane (4.0 ml), and thereto are added sodium iodide (857 mg), copper iodide (27 mg) and trans-N,N'-dimethylcyclohexane-1,2-diamine (43 mg), and the mixture is stirred at 110 °C under nitrogen atmosphere overnight. The mixture is allowed to cool to room temperature, and thereto is added a diluted aqueous ammonia, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 97:3→70:30) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-iodopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (969 mg). MS (m/z): 747 $[M+H]^+$

(2) To (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-iodopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) are added 2-methoxyethanol (1.0 ml), cesium carbonate (350 mg), copper iodide (23 mg) and 1,10-phenanthroline (44 mg), and the mixture is stirred at 110°C for 4 days. The mixture is allowed to cool to room temperature, and thereto is added water, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 10:1, and NH-silica gel: hexane:ethyl acetate = 10:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-

benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (90 mg, MS (m/z): 695 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)primidin-2-yl]iodopyrimidin-2-yl}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-methoxyethyl ester (28 mg, MS (m/z): 725 $[M+H]^+$).

Example 25

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1 g), 6-chloronicotinonitrile (1.76 g), diisopropylethylamine (804 µl) are dissolved in N,N-dimethylformamide (15 ml), and the mixture is stirred at 100°C overnight. The reaction solution is cooled to room temperature, and thereto are added an aqueous citric acid solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel, chloroform:hexane:ethyl acetate = 5:5:1) to give (2R,4S)-4-(5-cyanopyridin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (800 mg). MS (m/z): 419 $[M+H]^+$

(2) (2R,4S)-4-(5-Cyanopyridin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (790 mg) and 3,5-bis-(trifluoromethyl)benzyl bromide (1.159 g) are dissolved in N,N-dimethylformamide (9 ml), and thereto is added sodium hydride (62.7 %, 108 mg) at room temperature, and the mixture is further stirred for 15 minutes. To the reaction solution is added acetic acid, and thereto are added a saturated brine and ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 19:1→17:8) to give (2R,4S)-4-{[3,5-bis-(trifluoromethyl)benzyl]-(5-cyanopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (700 mg).

MS (m/z): 645 $[M+H]^+$

Example 26

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-cyanopyridin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (127 mg), sodium azide (300 mg) and ammonium chloride (300 mg) are dissolved in N,N-dimethylformamide (5 ml), and the mixture is stirred at 95°C overnight. The mixture is allowed to cool to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(tetrazol-5-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (128 mg). MS (m/z) 688 $[M+H]^+$

Example 27

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.5 g) and 2-chloro-5-nitropyridine (3.795 g) are dissolved in 1,3-dimethylimidazolidinone (25 ml), and the mixture is stirred at 140°C for 74 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; chloroform→hexane: ethyl acetate = 3:1) to give (2R,4S)-2-ethyl-4-(5-nitropyridin-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (991 mg). MS (m/z): 439 $[M+H]^+$

(2) (2R,4S)-2-Ethyl-4-(5-nitropyridin-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (980 mg) and 3,5-bis(trifluoromethyl)benzyl bromide (1.372 g) are dissolved in N,N-dimethylformamide (10 ml), and thereto is added sodium hydride (62.7 %, 171 mg) at room temperature, and the mixture is stirred for 15 minutes. To the

reaction solution is added acetic acid, and thereto are added water and ethyl acetate. The organic layer is washed again with water, and the organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 49:1→13:7) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-nitropyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (650 mg) MS (m/z): 665 $[M+H]^+$

Example 28

(1) (2R,4S)-4-[3,5-Bis(trifluoromethyl)benzyl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (600 mg) is dissolved in ethanol (5.0 ml), and thereto are added cyanogen bromide (129 mg) and sodium hydrogen carbonate (283 mg), and the mixture is stirred at room temperature for 23 hours and 15 minutes. Distilled water is added to the mixture, and the mixture is extracted with ether. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]cyano}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (581 mg). MS (m/z): 585 $[M+H_2O]^+$

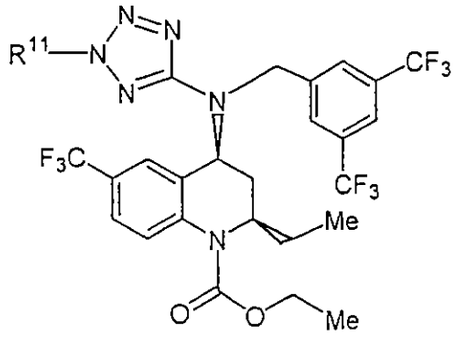
(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]cyano}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (50 mg) is dissolved in N,N-dimethylformamide (1 ml), and thereto are added sodium azide (57.2 mg) and ammonium chloride (47.1 mg), and the mixture is stirred at 100°C for 16.5 hours. The mixture is allowed to cool to room temperature, and thereto is added distilled water, and the mixture is extracted with ethyl acetate. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; chloroform:methanol =

9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(tetrazol-5-yl)amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (45 mg). MS (m/z): 611 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(tetrazol-5-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (150 mg) is dissolved in tetrahydrofuran (2.5 ml), and thereto is added sodium hydride (62.7 %, 9.6 mg), and the mixture is stirred for 10 minutes. To the mixture is added propane 1-bromide (23 µl), and the mixture is stirred for 27 hours. Distilled water is added to the mixture, and the mixture is extracted with ethyl acetate. The extract is washed with a saturated brine, and the organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 10:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(2-propyl-2H-tetrazol-5-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (26 mg). MS (m/z): 653 $[M+H]^+$

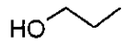
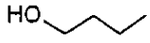
Examples 29-30

The corresponding starting compounds are treated in a similar manner to Example 28-(3) to give the compounds as listed in Table 3.



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Table 3

Example	R^{11}	Physical properties, etc.
29		MS (m/z): 655 $[M+H]^+$
30		MS (m/z): 669 $[M+H]^+$

Example 31

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(tetrazol-5-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) is dissolved in N,N-dimethylformamide (1 ml), and thereto are added 3-bromopropionic acid methyl ester (103.6 µl), triethylamine (2 ml) and a catalytic amount of potassium iodide, and the mixture stirred at 70°C for 48 hours. Distilled water is added to the mixture, and the mixture is extracted with ether. The extract is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2-methoxycarbonylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (581 mg). MS (m/z): 697 $[M+H]^+$

Examples 32-34

The corresponding starting compounds are treated in a similar manner to Example 31 to give the compounds as listed in Table 4.

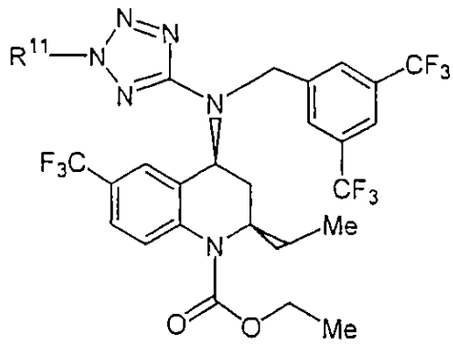
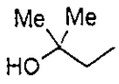
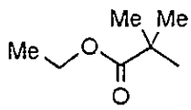
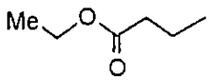


Table 4

Example	R^{11}	Physical properties, etc.
32		MS (m/z): 683 $[M+H]^+$
33		MS (m/z): 725 $[M+H]^+$
34		MS (m/z): 697 $[M+H]^+$

Example 35

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(tetrazol-5-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in tetrahydrofuran (5 ml), and thereto are added 2-dimethylaminoethanol (50 µl), a 40 % solution of diethyl azodicarboxylate in toluene (220 µl) and triphenylphosphine (131.1 mg), and the mixture is stirred at room temperature for 1.5 hours. Distilled water is added thereto, and the mixture is extracted with ethyl acetate. The extract is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2-dimethylaminoethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (155 mg). MS (m/z): 682 $[M+H]^+$

Examples 36-45

The corresponding starting compounds are treated in a similar manner to Example 35 to give the compounds as listed in Table 5.

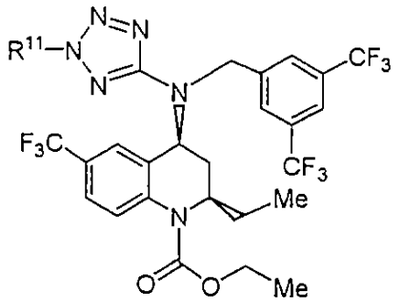
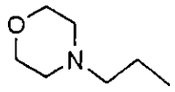
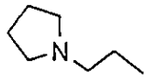
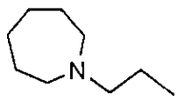
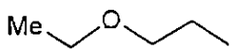
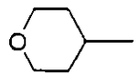
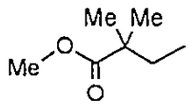
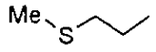
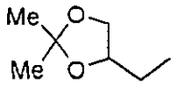
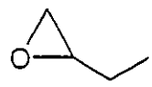
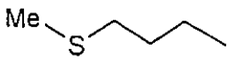


Table 5

Example	R^{11}	Physical properties, etc.
36		MS (m/z): 724 $[M+H]^+$
37		MS (m/z): 708 $[M+H]^+$
38		MS (m/z): 736 $[M+H]^+$
39		MS (m/z): 683 $[M+H]^+$
40		MS (m/z): 695 $[M+H]^+$
41		MS (m/z): 725 $[M+H]^+$
42		MS (m/z): 685 $[M+H]^+$
43		MS (m/z): 725 $[M+H]^+$

44		MS (m/z): 667 [M+H]+
45		MS (m/z): 699 [M+H]+

Example 46

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-methoxycarbonyl-2-methylpropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) is dissolved in a mixture of ethanol (3 ml) and distilled water (0.5 ml), and thereto is added lithium hydroxide monohydrate (34.7 mg) under ice-cooling. The mixture is stirred at room temperature for 4 days, and thereto is added a saturated aqueous citric acid solution, and the mixture is extracted with methylene chloride. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 2:1→1:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-[2-(2-carboxy-2-methylpropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (262 mg) MS (m/z): 709 [M-H]-

Examples 47-49

The corresponding starting compounds are treated in a similar manner to Example 46 to give the compounds as listed in Table 6

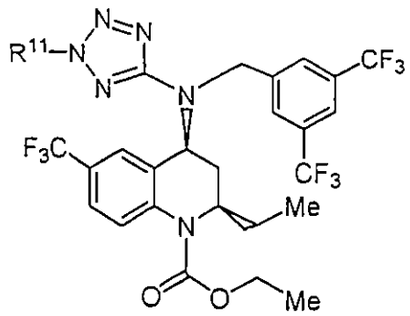
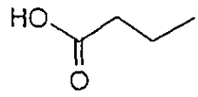
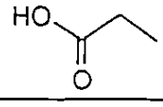
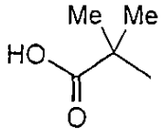


Table 6

Example	R^{11}	Physical properties, etc.
47		MS (m/z):683 $[M+H]^+$
48		MS (m/z):669 $[M+H]^+$
49		MS (m/z):697 $[M+H]^+$

Example 50

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(3-methylthiopropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (175 mg) is dissolved in chloroform (2 ml), and thereto is added m-chloroperbenzoic acid (422.8 mg), and the mixture is stirred at room temperature for 30 minutes. To the mixture is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure The resulting residue is purified by column chromatography (silica gel, hexane:ethyl acetate = 7:3→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(3-methanesulfonylpropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (180 mg). MS (m/z): 731 $[M+H]^+$

Example 51

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-methylthioethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in chloroform (2 ml), and thereto is added m-chloroperbenzoic acid (100.1 mg), and the mixture is stirred at room temperature for 2.5 hours. To the mixture is added a

saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with methylene chloride. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; chloroform:methanol = 49:1→19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2-methanesulfinylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (91.9 mg, MS (m/z): 701 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2-methanesulfonylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (118.6 mg, MS (m/z): 717 $[M+H]^+$).

Example 52

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (260mg) is dissolved in ethanol (2 ml), and thereto is added Dowex [H^+-type] (manufactured by The Dow Chemical Company) (4 g), and the mixture is stirred at room temperature for 39.5 hours. The mixture is filtered by using methanol, and the filtrate is concentrated under reduced pressure The resulting residue is purified by column chromatography (silica gel, hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2,3-dihydroxypropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg). MS (m/z): 685 $[M+H]^+$

Example 53

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(2-oxolanylmethyl-2H-tetrazol-5-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) is dissolved in a solution which is previously prepared by adding sodium hydride (62.7 %, 0.6 mg) into ethanol (2 ml), and stirred at room temperature for 5 minutes, and the

mixture is stirred for 18 hours and 40 minutes. Distilled water is added thereto, and the mixture is extracted with ether. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-[2-(3-ethoxy-2-hydroxypropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (92.7 mg). MS (m/z): 713 $[M+H]^+$

Example 54

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(2-oxolanylmethyl-2H-tetrazol-5-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (120 mg) is dissolved in ethanol (1 ml), and thereto is added a 28 % aqueous ammonia (1 ml). The mixture is stirred at room temperature for 18.5 hours. The reaction solution is concentrated under reduced pressure, and the resulting residue is purified by column chromatography (silica gel; chloroform:methanol = 49:1→19:1) to give (2R,4S)-4-{[2-(3-amino-2-hydroxypropyl)-2H-tetrazol-5-yl]-[3,5-bis(trifluoro-methyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (51.2 mg). MS (m/z): 684 $[M+H]^+$

Examples 55-58

The corresponding starting compounds are treated in a similar manner to Example 54 to give the compounds as listed in Table 7.

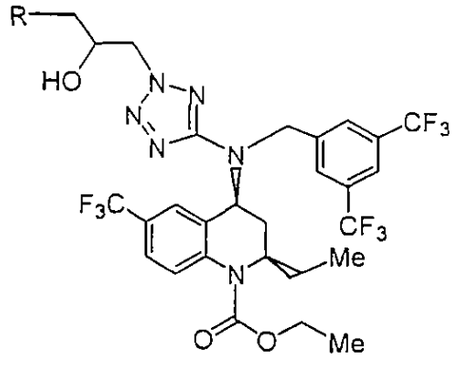
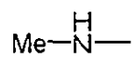
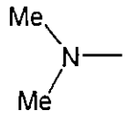
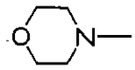
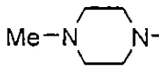


Table 7

Example	R	Physical properties, etc.
55		MS (m/z): 698 $[M+H]^+$
56		MS (m/z): 712 $[M+H]^+$
57		MS (m/z): 754 $[M+H]^+$
58		MS (m/z): 767 $[M+H]^+$

Example 59

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]cyano}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (15 g) is dissolved in ethanol (150 ml), and thereto are added hydroxylamine hydrochloride (2.1 g) and triethylamine (4.2 ml), and the mixture is stirred at room temperature for 18 hours. Distilled water is added to the mixture, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 19:1→7:3) to give (2R,4S)-4-{[amino(hydroxyimino)methyl]-[3.5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5.02 g). MS (m/z): 601 $[M+H]^+$

(2) (2R,4S)-4-{[Amino(hydroxyimino)methyl]-[3,5-bis(trifluoromethyl)-benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (60 mg) is dissolved in methylene chloride (1 ml) and thereto are added diisopropylethylamine (35 µl) and hexanoic acid chloride (18 µl), and the mixture is stirred for 16 hours. Distilled water is

added to the mixture, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 19:1→9:1) to give (2R,4S)-4-[(amino{[(1-oxohexyl)oxy]imino}methyl)-[3,5-bis(trifluoromethyl)benzyl]]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (60.6 mg). MS (m/z): 699 $[M+H]^+$

(3) (2R,4S)-4-[(Amino{[(1-oxohexyl)oxy]imino}methyl)-[3,5-bis(trifluoromethyl)benzyl]]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (37 mg) is dissolved in ethanol (1 ml), and thereto is added sodium methoxide (0.3 mg), and the mixture is stirred for one hour. Distilled water is added to the mixture, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-(5-pentyl-[1,2,4]oxadiazole-3-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (60.6 mg). MS (m/z): 681 $[M+H]^+$

Example 60

(2R,4S)-4-{[Amino(hydroxyimino)methyl]-[3,5-bis(trifluoromethyl)-benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (154 mg) is dissolved in methylene chloride (1.5 ml), and thereto are added diisopropylethylamine (89 µl) and methoxyacetic acid chloride (30 µl), and the mixture is stirred for 18 hours. Distilled water is added to the mixture, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 2:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-

benzyl]-{5-methoxymethyl-[1,2,4]oxadiazol-3-yl}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (118.3 mg). MS (m/z): 655 $[M+H]^+$

Examples 61-63

The corresponding starting compounds are treated in a similar manner to Example 60 to give the compounds as listed in Table 8.

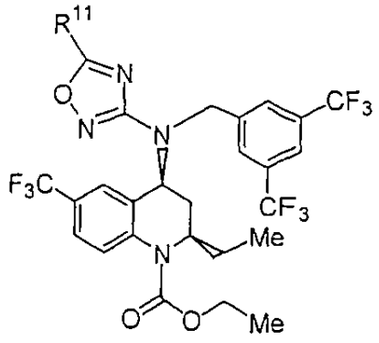
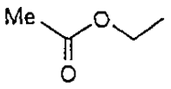
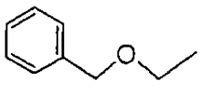


Table 8

Example	R^{11}	Physical properties, etc.
61		MS (m/z): 683 $[M+H]^+$
62		MS (m/z): 731 $[M+H]^+$
63		MS (m/z): 703/705 $[M+H]^+$

Example 64

(2R,4S)-4-{(5-Acetoxymethyl-[1,2,4]oxadiazol-3-yl)-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (30 mg) is dissolved in ethanol (1 ml), and thereto is added potassium carbonate (60.8 mg), and the mixture is stirred for 30 minutes. Distilled water is added, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel;

hexane:ethyl acetate = 4:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-(5-hydroxymethyl-[1,2,4]oxadiazol-3-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (22 mg). MS (m/z): 641 $[M+H]^+$

Example 65

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromomethyl-[1,2,4]-oxadiazol-3-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) is dissolved in a mixture of methanol (0.5 ml) and tetrahydrofuran (0.5 ml), and thereto is added morpholine (0.1 ml). The mixture is stirred at 45°C for 2 hours. The mixture is allowed to cool to room temperature, and thereto is added 1N hydrochloric acid, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure The resulting residue is purified by column chromatography (silica gel, hexane:ethyl acetate = 4:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)methyl-[1,2,4]oxadiazol-3-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (69 mg). MS (m/z): 710 $[M+H]^+$

Examples 66-67

The corresponding starting compounds are treated in a similar manner to Example 65 to give the compounds as listed in Table 9.

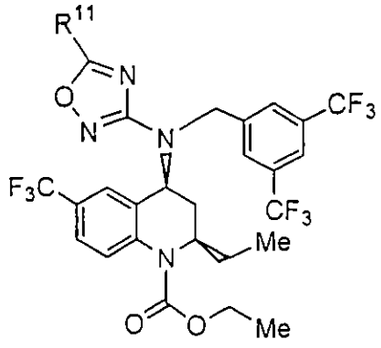
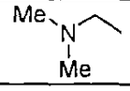
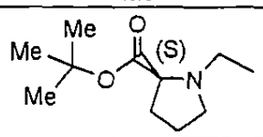


Table 9

Example	R^{11}	Physical properties, etc.
66		MS (m/z): 668 $[M+H]^+$
67		MS (m/z): 794 $[M+H]^+$

Example 68

(2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{[5-((2S)-2-tert-butoxycarbonylpyrrolidin-1-yl)methyl]-[1,2,4]oxadiazol-3-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (55 mg) is dissolved in a 4 N hydrochloride 1,4-dioxane solution (0.5 ml), and the mixture is stirred at room temperature overnight. The reaction solution is concentrated under reduced pressure, and the resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→chloroform) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{[5-((2S)-2-carboxypyrrolidin-1-yl)methyl]-[1,2,4]oxadiazol-3-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (27.5 mg). MS (m/z): 738 $[M+H]^+$

Example 69

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1 g), 4,6-dichloropyrimidine (1.9 g), and diisopropylamine (824 mg) are dissolved in N,N-dimethylformamide (15 ml), and the mixture is stirred at 80°C for 3 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 19:1→7:3) to give (2R,4S)-4-(6-chloropyrimidin-4-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

(1.088 g). MS (m/z): 429/431 $[M+H]^+$

(2) (2R,4S)-4-(6-Chloropyrimidin-4-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg), 3,5-bis-(trifluoromethyl)benzyl bromide (143 mg), and sodium hydride (62.7 %, 18 mg) are dissolved in N,N-dimethylformamide (2 ml), and the mixture is stirred at 55°C for 15 minutes. The reaction solution is cooled to room temperature, and thereto are added an aqueous citric acid solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 49:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(6-chloropyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (75 mg). MS (m/z): 655/657 $[M+H]^+$

(3) A mixture of (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(6-chloropyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (220 mg) and morpholine (4 ml) is stirred at 70°C for 20 minutes. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 19:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[6-(morpholin-4-yl)-pyrimidin-4-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (110 mg). MS (m/z): 706 $[M+H]^+$

Examples 70-75

The corresponding starting compounds are treated in a similar manner to Example 69-(3) to give the compounds as listed in Table 10.

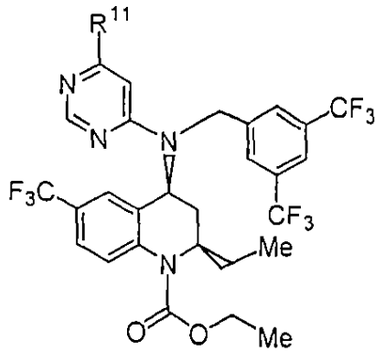
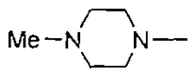
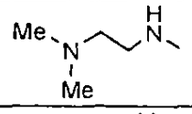
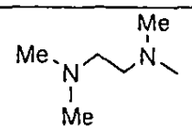
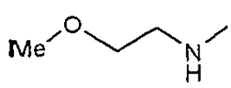
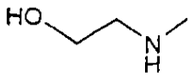
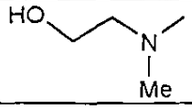


Table 10

Example	R^{11}	Physical properties, etc.
70		MS (m/z): 719 $[M+H]^+$
71		MS (m/z): 707 $[M+H]^+$
72		MS (m/z): 721 $[M+H]^+$
73		MS (m/z): 708 $[M+H]^+$
74		MS (m/z): 680 $[M+H]^+$
75		MS (m/z): 694 $[M+H]^+$

Example 76

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1 g), 4-chloro-2-methylthio-pyrimidine (2.04 g), and diisopropylethylamine (890 µl) are dissolved in N,N-dimethylformamide (15 ml), and the mixture is stirred at 100 °C overnight. The reaction solution is cooled to room temperature, and thereto are added an aqueous citric acid solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium

sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→3:2) to give (2R,4S)-2-ethyl-4-(2-methylthiopyrimidin-4-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.07 g). MS (m/z): 441 $[M+H]^+$

(2) (2R,4S)-2-Ethyl-4-(2-methylthiopyrimidin-4-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.05 g) and 3,5-bis(trifluoromethyl)benzyl bromide (1.465 g) are dissolved in N,N-dimethylformamide (10 ml), and thereto is added sodium hydride (62.7 %, 137 mg) at room temperature, and the mixture is stirred for one hour. To the reaction solution is added acetic acid, and thereto are added water and ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(2-methylthiopyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.35 g). MS (m/z): 667 $[M+H]^+$

Example 77

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(2-methylthiopyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (133.2 mg) is dissolved in chloroform (3 ml), and thereto is added m-chloroperbenzoic acid (64.5 mg) at room temperature, and the mixture is stirred for 5 minutes. To the reaction solution is added NH-silica gel, and the NH-silica gel is removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→0:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(2-methylsulfinylpyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (53 mg. MS (m/z): 683 $[M+H]^+$) and (2R,4S)-4-{[3,5-

bis(trifluoromethyl)benzyl]-(2-methylsulfonylpyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (66 mg, MS (m/z): 699 $[M+H]^+$).

Example 78

Hydroxylamine hydrochloride (269 mg) is suspended in dimethylsulfoxide (3 ml), and thereto is added triethylamine (0.54 ml). The insoluble materials are collected by filtration, and washed with tetrahydrofuran. Tetrahydrofuran is removed from the filtrate by evaporation under reduced pressure to give a solution of hydroxylamine in dimethylsulfoxide. To this solution is added (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-cyanopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg), and the mixture is stirred at 75°C for 30 minutes. The mixture is allowed to cool to room temperature, and to the reaction solution are added ethyl acetate and a saturated brine. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(N-hydroxycarbamimidoyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (520 mg). MS (m/z): 679 $[M+H]^+$

Example 79

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(2-methylsulfonyl-pyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) and an excess amount of 2-amino-ethanol are dissolved in 1,3-dimethylimidazolidinone (2 ml), and the mixture is stirred at 90°C for one hour. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate =3:2→1:4) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2-hydroxy-

ethylamino)pyrimidin-4-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (7.2 mg). MS (m/z): 680 $[M+H]^+$

Examples 80-82

The corresponding starting compounds are treated in a similar manner to Example 79 to give the compounds as listed in Table 11.

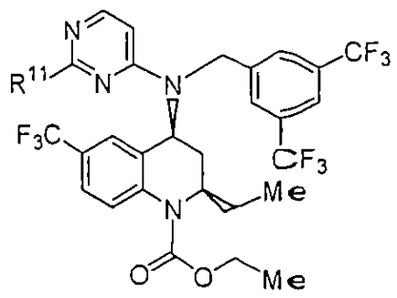
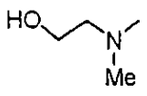
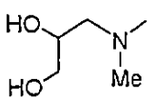
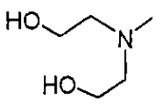


Table 11

Example	R^{11}	Physical properties, etc.
80		MS (m/z): 694 $[M+H]^+$
81		MS (m/z): 724 $[M+H]^+$
82		MS (m/z): 724 $[M+H]^+$

Example 83

4-Methoxybenzyl alcohol (136 mg) is dissolved in N,N-dimethylformamide (3 ml), and thereto is added sodium hydride (62.7 %, 42 mg) at room temperature, and the mixture is stirred for 30 minutes. To the reaction mixture is further added (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-(2-methylsulfonylpyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (686 mg), and the mixture is stirred for 5 hours. Acetic acid is added to the reaction solution,

and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(4-methoxybenzyloxy)-pyrimidin-4-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (600 mg). MS (m/z): 757 $[M+H]^+$

Example 84

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(4-methoxybenzyloxy)-pyrimidin-4-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (570 mg) is dissolved in 1,4-dioxane (4 ml), and thereto is added conc. hydrochloric acid (4 ml) at room temperature. The reaction solution is stirred for 15 minutes, and neutralized with a saturated aqueous sodium hydrogen carbonate solution. Ethyl acetate is added to the reaction solution, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 1:1→0:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(2-hydroxypyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (410 mg). MS (m/z): 637 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(2-hydroxypyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (376 mg), 2-iodoethanol (305 mg), and cesium carbonate (1.152 g) are dissolved in N,N-dimethylformamide (5 ml), and the mixture is stirred at 60°C for 3 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 1:1→0:1),

further by column chromatography (silica gel; hexane:ethyl acetate = 3:7→0:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyrimidin-4-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (240 mg, MS (m/z): 681 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{1-[2-(2-hydroxyethoxy)ethyl]-2-oxo-1,2-dihydropyrimidin-4-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (7 mg, MS (m/z): 725 $[M+H]^+$).

Example 86

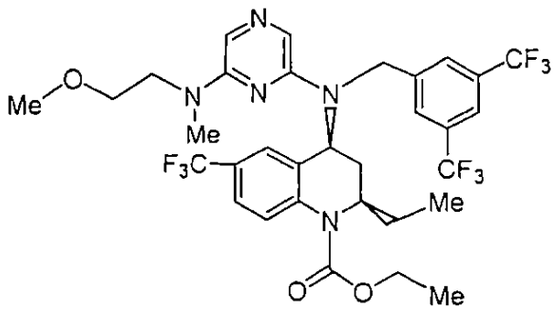
(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5 g) is dissolved in toluene (50 ml). and thereto are added tris(dibenzylideneacetone)dipalladium (293 mg), sodium tert-butoxide (3.8 g), 2-(di-tert-butylphosphino)biphenyl (376 mg). and 2,6-dichloropyrazine (4.7 g). The mixture is stirred at room temperature under nitrogen atmosphere for 23 hours. To the mixture is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ether. The organic layer is washed with a saturated brine. dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 6:1→3:1) to give (2R,4S)-4-(6-chloropyrazin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5.3 g). MS (m/z): 429 $[M+H]^+$

(2) (2R,4S)-4-(6-Chloropyrazin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3 g) is dissolved in N,N-dimethylformamide (35 ml), and thereto are added sodium hydride (62.7 %, 348 mg) and 3,5-bis(trifluoromethyl)benzyl bromide (9 mL), and the mixture is stirred at room temperature for 48 hours. Distilled water is added to the mixture, and the mixture is extracted with ether. The organic layer is washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by

column chromatography (silica gel; hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(6-chloropyrazin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.6 g). MS (m/z): 655 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(6-chloropyrazin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in 1,3-dimethylimidazolidinone (2 ml), and thereto are added diisopropylethylamine (80 µl) and morpholine (140 µl). The mixture is stirred at 80°C for 51 hours, and allowed to cool to room temperature. A saturated aqueous citric acid solution is added to the mixture, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→3:7) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[6-(morpholin-4-yl)pyrazin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (132.8 mg). MS (m/z): 706 $[M+H]^+$

Example 87



The corresponding starting compound is treated in a similar manner to Example 86 to give the compound of Example 87. MS (m/z): 708 $[M+H]^+$

Example 88

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) and 2-chloro-5-nitrothiazole (416 mg) are dissolved in N,N-dimethylformamide (1 ml), and the

mixture is stirred at 100°C for 3 hours. The reaction solution is cooled to room temperature, and thereto are added an aqueous citric acid solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-2-ethyl-4-(5-nitorthiazol-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (148 mg). MS (m/z): 445 $[M+H]^+$

(2) (2R,4S)-2-Ethyl-4-(5-nitrothiazol-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (133 mg) and 3.5-bis(trifluoromethyl)benzyl bromide (179 mg) are dissolved in tetrahydrofuran (3 ml), and thereto is added sodium hydride (62.7 %, 34 mg), and the mixture is stirred at room temperature overnight. To the reaction solution is added acetic acid, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→2:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-nitrothiazol-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (58 mg). MS (m/z): 671 $[M+H]^+$

Example 89

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]cyano}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (327.9 mg) is dissolved in tetrahydrofuran (3 ml), and thereto is added sodium hydride (62.7 %, 13.9 mg). The mixture is stirred with ice-cooling under nitrogen atmosphere for one hour. To the reaction solution is slowly added dropwise a solution of 3-buten-1-ol (41.8 mg) in tetrahydrofuran (4 ml) under ice-cooling, and the mixture is stirred at room temperature for 29 hours. Distilled water is added under ice-cooling, and the mixture is extracted with ethyl acetate. The organic layer is dried over magnesium

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sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1) to give (2R,4S)-4-{1-[3,5-bis(trifluoromethyl)benzyl]-2-(3-buten-1-yl)}isoureido-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (186.3 mg). MS (m/z): 640 $[M+H]^+$

(2) (2R,4S)-4-{1-[3,5-Bis(trifluoromethyl)benzyl]-2-(3-buten-1-yl}isoureido-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (172 mg) is dissolved in chloroform (3 ml), and thereto is added N-iodosuccimide (72.5 mg). The mixture is stirred at room temperature for 1.5 hours, and thereto is added a saturated aqueous sodium thiosulfate solution. The mixture is extracted with ether, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(4-iodomethyl-5,6-dihydro-4H-[1,3]oxadin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (211 mg). MS (m/z): 766 $[M+H]^+$

Example 90

(1) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) is dissolved in N,N-dimethylformamide (1 ml), and thereto is added sodium hydride (62.7 %, 10.3 mg), and the mixture is stirred with ice-cooling under nitrogen atmosphere for 10 minutes. 3,5-Dimethoxybenzyl bromide (74 mg) is added to the mixture under ice-cooling, and the mixture is stirred at room temperature for 16.5 hours. Distilled water is added to the mixture under ice-cooling, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-[(5-bromopyrimidin-2-yl)-(3,5-dimethoxybenzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-

carboxylic acid ethyl ester (95.1 mg). MS (m/z): 623/625 $[M+H]^+$

(2) (2R,4S)-4-[(5-Bromopyrimidin-2-yl)-(3,5-dimethoxybenzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (290 mg) is dissolved in toluene (4 ml), and tris(dibenzylidene-acetone)dipalladium (8.5 mg), sodium tert-butoxide (68.2 mg), 2-(di-tert-butylphosphino)biphenyl (11 mg) and morpholine (62 µl) are added thereto. The reaction mixture is stirred under nitrogen atmosphere at room temperature for 4 days. The reaction solution is stirred at 80°C for 5.5 hours, and allowed to cool to room temperature. Distilled water is added to the mixture, and the mixture is extracted with ether. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 4:1—3:2) to give (2R,4S)-4-{(3,5-dimethoxybenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (141.5 mg) MS (m/z): 630 $[M+H]^+$

Examples 91-94

The corresponding starting compounds are treated in a similar manner to Example 90 to give the compounds as listed in Table 12.

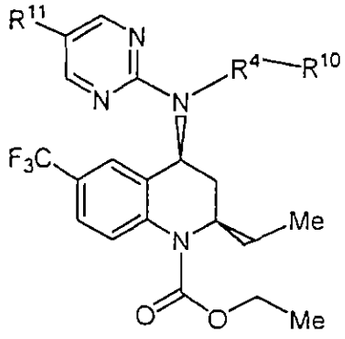
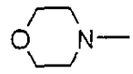
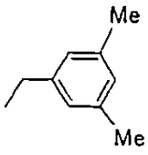
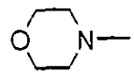
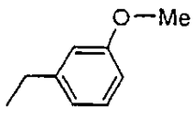
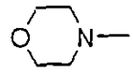
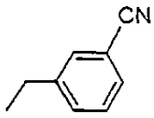
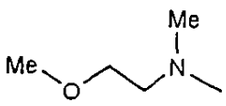
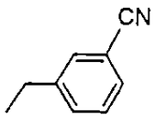


Table 12

Example	R^{11}	R^9-R^{10}	Physical properties, etc.
91			MS (m/z): 598 $[M+H]^+$
92			MS (m/z): 600 $[M+H]^+$
93			MS (m/z): 595 $[M+H]^+$
94			MS (m/z): 597 $[M+H]^+$

Example 95

(1) 6-Bromopyridin-2-carbaldehyde (5 g) is dissolved in a mixture of methanol (10 ml) and tetrahydrofuran (15 ml), and thereto is added sodium borohydride (3.05 g) at 0°C, and the mixture is stirred for 10 minutes. To the reaction solution are added an aqueous citric acid solution and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→2:3) to give (6-bromopyridin-2-yl)methanol (3.92 g). MS (m/z): 188/190 $[M+H]^+$

(2) (6-Bromopyridin-2-yl)methanol (3.9 g) and triphenylphosphine (7.6 g) are dissolved in methylene chloride (50 ml), and thereto is added carbon tetrabromide (8.25 g) under ice-cooling. The reaction solution is concentrated under reduced pressure, and the resulting residue is purified

by column chromatography (silica gel; hexane:ethyl acetate = 49:1→47:3) to give 2-bromo-6-bromomethylpyridine (2.96 g). MS (m/z): 250/252 $[M+H]^+$

(3) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (400 mg) is dissolved in N,N-dimethylformamide (4 ml), and thereto is added at 10°C sodium hydride (62.7 %, 42 mg). The mixture is stirred at the same temperature for 10 minutes, and to the reaction solution is added 2-bromo-6-bromomethylpyridine (318 mg). The mixture is stirred at the same temperature for 15 minutes, and thereto is added acetic acid. A saturated aqueous sodium hydrogen carbonate solution and ethyl acetate are added to the mixture. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 48:2→3:2) to give (2R,4S)-4-[(6-bromo-pyridin-2-yl)methyl-(5-bromopyrimidin-2-yl)]amino-2-ethyl-6-trifluoro-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (470 mg). MS (m/z): 642/644 $[M+H]^+$

(4) (2R,4S)-4-[(6-bromopyridin-2-yl)methyl-(5-bromopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (150 mg), tetrakis(triphenylphosphine)palladium (28 mg) and zinc cyanide (71.2 mg) are dissolved in N,N-dimethylformamide (3 ml), and the mixture is stirred at 95°C under nitrogen atmosphere overnight. The reaction solution is cooled to room temperature, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 47:3→2:3) to give (2R,4S)-4-[(6-cyanopyridin-2-yl)methyl-(5-cyanopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl

ester (105 mg). MS (m/z): 536 $[M+H]^+$

Examples 96-97

(2R*,4S*)-4-Amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is treated in a similar manner to Example 1 to give the compounds as listed in Table 13.

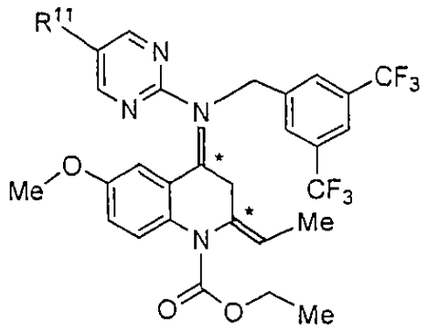
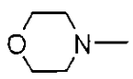
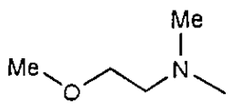
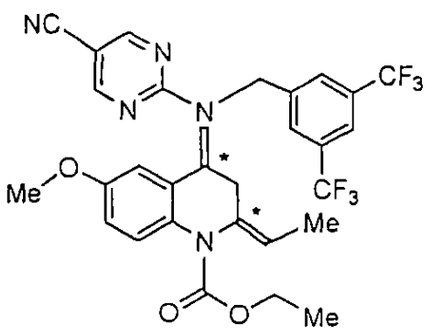


Table 13

Example	Configuration	R^{11}	Physical properties, etc.
96	(2R*,4S*)		MS (m/z): 668 $[M+H]^+$
97	(2R*,4S*)		MS (m/z): 670 $[M+H]^+$

Example 98



The corresponding starting compound is treated in a similar manner to Example 10 to give the compound of Example 98. MS (m/z): 608 $[M+H]^+$

Example 99

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (284 mg), acrylic acid benzyl ester (125 mg), tris(dibenzylideneacetone)dipalladium (292 mg), dicyclohexylmethylamine (110 µl), and tri(tert-butyl)phosphonium tetrafluoroborate (308 mg) are dissolved in 1,4-dioxane (4 ml), and the mixture is stirred at room temperature under nitrogen atmosphere overnight. The reaction solution is concentrated under reduced pressure, and the resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 9:1→4:1) to give (2R*,4S*)-4-{[5-(2-benzyloxycarbonylvinyl)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (266 mg). MS (m/z): 743 $[M+H]^+$

Example 100

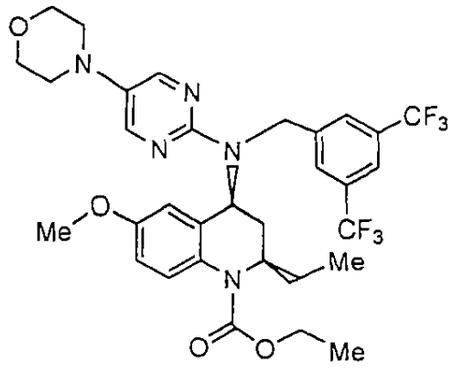
(2R*,4S*)-4-{[5-(2-Benzyloxycarbonylvinyl)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (265 mg) is dissolved in a mixture of methanol (4 ml) and tetrahydrofuran (1 ml), and thereto is added a catalytic amount of 10 % palladium-carbon, and the mixture is stirred at room temperature under hydrogen atmosphere for 3 hours. The catalyst (10 % palladium-carbon) is removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-carboxyvinyl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (176 mg). MS (m/z): 653 $[M+H]^+$

Example 101

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-carboxyvinyl)-pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (120 mg) is dissolved in a mixture of methanol (4

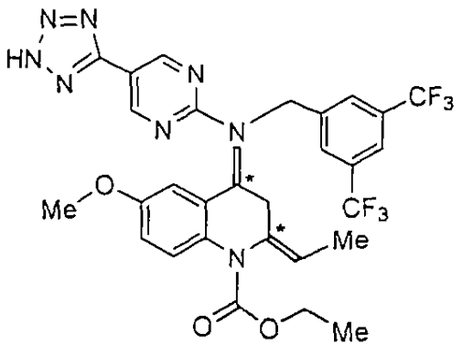
ml) and tetrahydrofuran (1 ml), and a catalytic amount of 10 % palladium-carbon is added thereto, and the mixture is stirred at room temperature under hydrogen atmosphere overnight. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-carboxyethyl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (35 mg). MS (m/z): 655 $[M+H]^+$

Example 102



(2R,4S)-4-Amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is treated in a similar manner to Example 1 to give the compound of Example 102. MS (m/z): 668 $[M+H]^+$

Example 103



The corresponding starting compound is treated in a similar manner

to Example 19 to give the compound of Example 103. MS (m/z): 651 $[M+H]^+$

Examples 104-105

The corresponding starting compounds are treated in a similar manner to Example 20 to give the compounds as listed in Table 14.

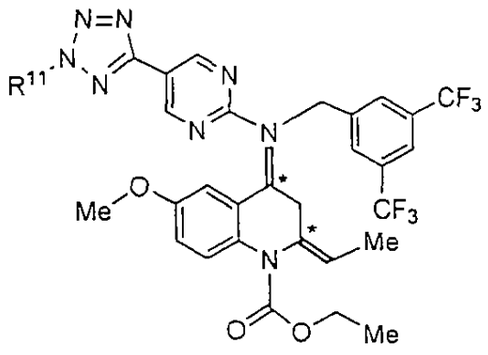
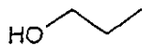


Table 14

Example	Configuration	R^{11}	Physical properties, etc.
104	(2R*,4S*)	CH_3-	MS (m/z): 665 $[M+H]^+$
105	(2R*,4S*)		MS (m/z): 695 $[M+H]^+$

Examples 106-109

The corresponding starting compounds are treated in a similar manner to Example 35 to give the compounds as listed in Table 15.

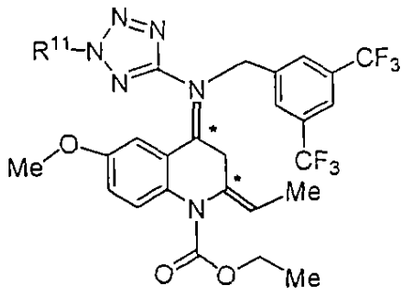
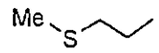
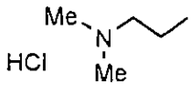
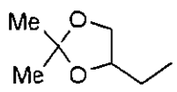
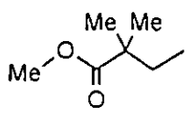


Table 15

Example	Configuration	R^{11}	Physical properties, etc.
106	(2R*,4S*)		MS (m/z): 647 $[M+H]^+$
107	(2R*,4S*)		MS (m/z): 644 $[M+H]^+$
108	(2R*,4S*)		MS (m/z): 687 $[M+H]^+$
109	(2R*,4S*)		MS (m/z): 687 $[M+H]^+$

Example 110

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-methylthioethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (226 mg) is dissolved in methylene chloride (3 ml), and thereto is added m-chloroperbenzoic acid (75 mg) at room temperature, and the mixture is stirred overnight To the reaction solution is added an aqueous potassium carbonate solution, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; chloroform:methanol = 1:0—20:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2-methylsulfinylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (176 mg). MS (m/z): 663 $[M+H]^+$

Example 111

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-methylsulfinyl-ethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (117 mg) is dissolved in methylene

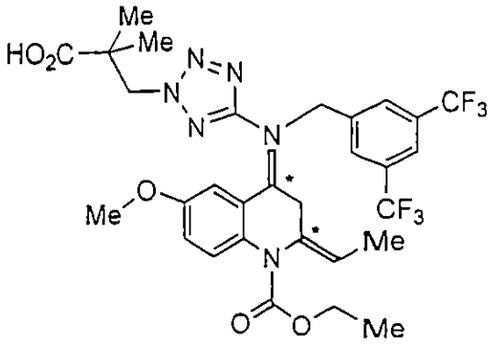
chloride (2 ml), and thereto is added m-chloroperbenzoic acid (76 mg) at room temperature. The mixture is stirred overnight, and to the reaction solution is added an aqueous potassium carbonate solution. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 2:1→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2-methylsulfonylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (108 mg). MS (m/z): 679 $[M+H]^+$

Example 112

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2,2-dimethyl-[1,3]-dioxolan-4-ylmethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (129 mg) is dissolved in a mixture of methanol (3 ml) and water (0.3 ml), and thereto are added at room temperature a strongly acidic resin (IR-120, manufactured by Organo Corporation) (50 mg) and a 6N hydrochloric acid (2 ml), and the mixture is stirred overnight. The resin is removed by filtration, and to the filtrate are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[2-(2,3-dihydroxypropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (123 mg). MS (m/z): 647 $[M+H]^+$

Example 113

The corresponding starting compound is treated in a similar manner to Example 46 to give the compound of the following formula. MS (m/z): 673 $[M+H]^+$



Examples 114-115

The corresponding starting compounds are treated in a similar manner to Example 60 to give the compounds as listed in Table 16.

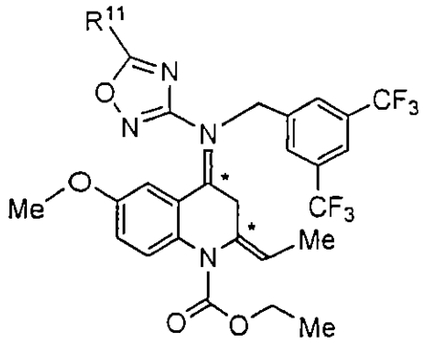
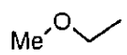
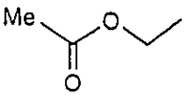
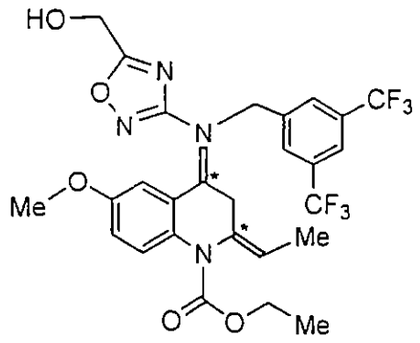


Table 16

Example	Configuration	R^{11}	Physical properties, etc.
114	(2R*,4S*)		MS (m/z): 634 $[M+H_2O]^+$
115	(2R*,4S*)		MS (m/z): 662 $[M+H_2O]^+$

Example 116

The corresponding starting compound is treated in a similar manner to Example 64 to give the compound of the following formula. MS (m/z): 620 $[M+H_2O]^+$

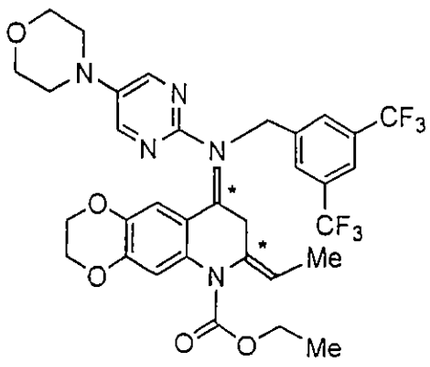


Example 117

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-bromopyrimidin-2-yl]}amino-6-bromo-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.48 g), tris(dibenzylideneacetone)dipalladium (190 mg), sodium tret-butoxide (401 mg), 2-(di-tert-butylphosphino)biphenyl (124 mg), and morpholine (197 µl) are dissolved in toluene (15 ml), and the mixture is stirred under nitrogen atmosphere at room temperature for 96 hours. To the reaction solution are added a saturated brine and ethyl acetate, and the organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 9:1→67:33) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-(morpholin-4-yl)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (320 mg, MS (m/z): 723 $[M+H]^+$) and (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-6-bromo-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (568 mg, MS (m/z): 716/718 $[M+H]^+$).

Example 118

The corresponding starting compound is treated in a similar manner to Example 1 to give the compound of the following formula. MS (m/z): 696 $[M+H]^+$



Example 119

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(N-hydroxy-carbamimidoyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) and 1,1'-carbonyldimidazole (72 mg) are dissolved in acetonitrile (5 ml), and the mixture is refluxed for 2 hours. The mixture is allowed to cool to room temperature, and to the reaction solution are added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(5-oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (60 mg) MS (m/z): 705 $[M+H]^+$

Example 120

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.83 g), copper(I) iodide (150 mg), sodium iodide (2.36 g), and N,N'-dimethylethylenediamine (168 µl) are dissolved in 1,4-dioxane (8 ml), and the mixture is stirred at 105°C under nitrogen atmosphere for 23 hours. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under

reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→6:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-iodopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.70 g). MS (m/z): 747 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-iodopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.69 g), sodium 3-methoxy-3-oxopropane-1-sulfinate (1.58 g), and copper(I) iodide (1.72 g) are dissolved in dimethylsulfoxide (20 ml), and the mixture is stirred at 110°C under nitrogen atmosphere for 2.5 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The precipitated insoluble materials are removed by filtration through Celite™, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→2:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-methoxycarbonylethanesulfonyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.41 g) MS (m/z): 771 $[M+H]^+$

Examples 121-123

The corresponding starting compounds are treated in a similar manner to Example 1-(3) to give the compounds as listed in Table 17.

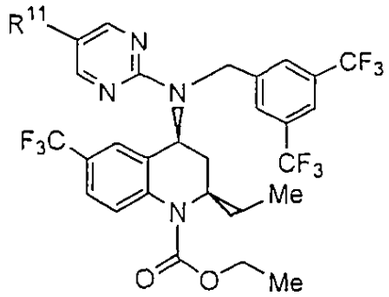
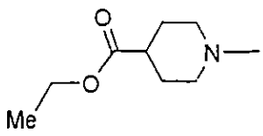
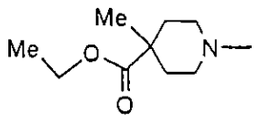
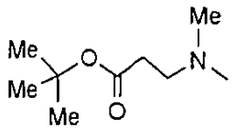


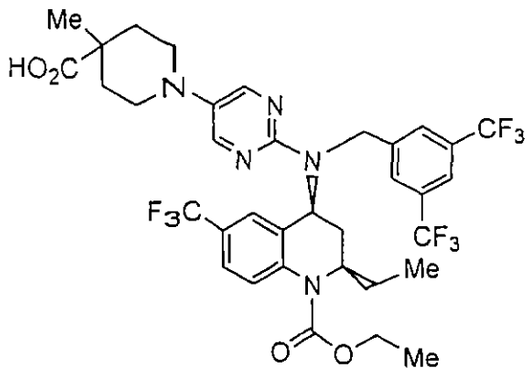
Table 17

Example	R^{11}	Physical properties, etc.
121		MS (m/z): 776 $[M+H]^+$
122		MS (m/z): 790 $[M+H]^+$
123		MS (m/z): 778 $[M+H]^+$

Example 124

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (265 mg) is dissolved in ethanol (3 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.342 ml), and the mixture is stirred at 50°C for one hour. The mixture is cooled to room temperature, and the reaction solution is acidified with 1N hydrochloric acid. The mixture is extracted with ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform: methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-carboxypiperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (241 mg). MS (m/z): 748 $[M+H]^+$

Example 125

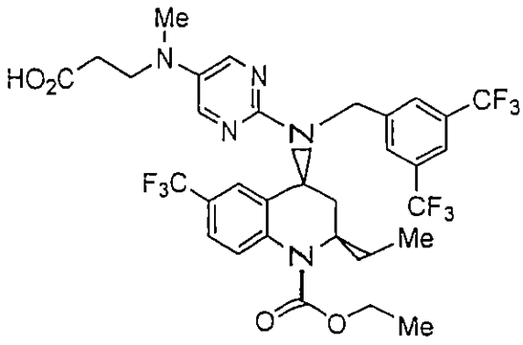


The corresponding starting compound is treated in a similar manner to Example 124 to give the compound of Example 125. MS (m/z): 762 $[M+H]^+$

Example 126

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxycarbonyl-ethanesulfonyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (700 mg) and a 2N aqueous sodium hydroxide solution (1.8 ml) are dissolved in ethanol (10 ml), and the mixture is stirred at 50°C for 30 minutes. The reaction solution is cooled to room temperature, and thereto are added a 2N aqueous hydrochloric acid solution (1.8 ml) and ethyl acetate under ice-cooling. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 99:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoro-methyl)benzyl]-(5-sulfopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (384 mg). MS (m/z): 699 $[M-H]^-$

Example 127



The corresponding starting compound is treated in a similar manner to Example 68 to give the compound of Example 127. MS (m/z): 722 $[M+H]^+$

Example 128

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-sulfopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (225 mg) is dissolved in thionyl chloride (5 ml), and the mixture is stirred at 80°C for 2 hours. The reaction solution is cooled to room temperature, and concentrated under reduced pressure. To the resulting residue is added chloroform (3 ml), and thereto is added a 2 N solution of methyl amine in tetrahydrofuran (3 ml) under ice-cooling. The mixture is stirred at room temperature for 2 hours, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→2:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-methylsulfamoylpyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (68 mg). MS (m/z): 714 $[M+H]^+$

Example 129

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-sulfopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (584 mg) is dissolved in thionyl chloride (5 ml), and the

mixture is stirred at 80°C for 2 hours. The reaction solution is cooled to room temperature, and concentrated under reduced pressure. To the resulting residue is added chloroform (3 ml), and thereto is further added a 7N solution of ammonia in methanol (3 ml) under ice-cooling. The mixture is stirred at room temperature for 2 hours, and water and ethyl acetate are added thereto. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→2:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-methoxysulfinylpyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (340 mg, MS (m/z): 699 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-sulfamoylpyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (22 mg, MS (m/z): 700 $[M+H]^+$).

Examples 130-133

The corresponding starting compounds are treated in a similar manner to Example 90 to give the compounds as listed in Table 18.

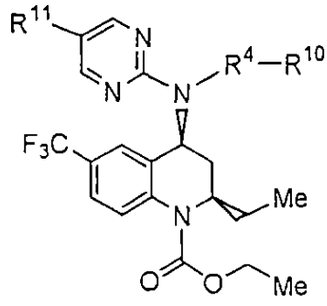
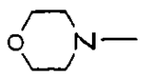
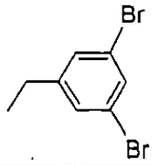
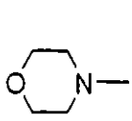
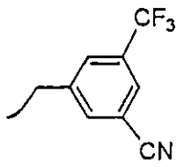
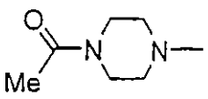
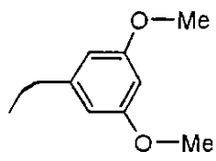
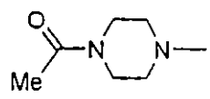
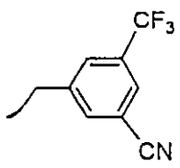


Table 18

Example	R^{11}	R^4-R^{10}	Physical properties, etc.
130			MS (m/z): 726/728/730 $[M+H]^+$

131			MS (m/z): 663 [M+H]+
132			MS (m/z): 671 [M+H]+
133			MS (m/z): 704 [M+H]+

Example 134

(2R,4S)-4-{(3,5-Dibromobenzyl)-[(5-morpholin-4-yl)pyrimidin-2-yl]}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in N,N-dimethylformamide (4 ml), and thereto are added zinc cyanide (71 mg) and a catalytic amount of tetrakis-(triphenylphosphine)palladium, and the mixture is stirred at 110°C under nitrogen atmosphere for 2.5 hours. The mixture is allowed to cool to room temperature, and thereto is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{(3,5-dicyanobenzyl)-[(5-morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (124 mg). MS (m/z): 620 [M+H]+

Examples 135-136

The corresponding starting compounds are treated in a similar manner to Example 99 to give the compounds as listed in Table 19.

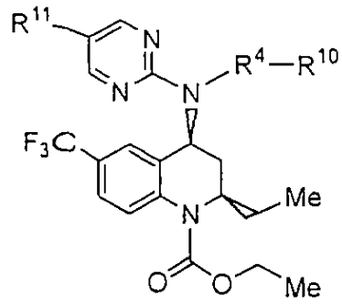
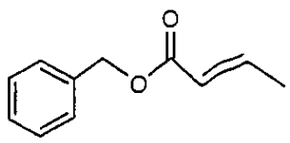
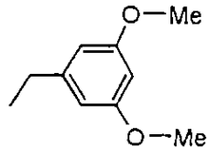
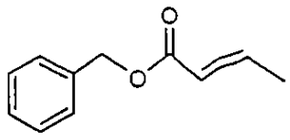
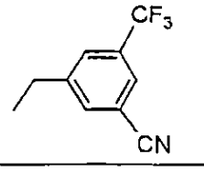


Table 19

Example	R^{11}	R^4-R^{10}	Physical properties, etc.
135			MS (m/z): 705 $[M+H]^+$
136			MS (m/z): 738 $[M+H]^+$

Example 137

(1) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (18 g) is dissolved in tetrahydrofuran (180 ml), and thereto are added di-tert-butyl dicarbonate (12.4 g) and a catalytic amount of 4-dimethylaminopyridine, and the mixture is stirred at room temperature overnight. To the reaction solution is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 8:1) to give (2R,4S)-4-[(tert-butoxycarbonyl)-(5-bromopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (22.5 g). MS (m/z): 473/475 $[M+H]^+$

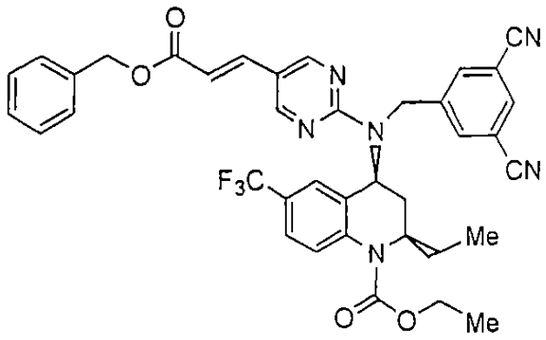
(2) (2R,4S)-4-[(tert-Butoxycarbonyl)-(5-bromopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5 g) is dissolved in 1,4-dioxane (60 ml), and thereto are added acrylic acid benzyl ester (2.83 g), tris(dibenzylideneacetone)dipalladium (1.2 g), tri(tert-butyl)phosphonium tetrafluoroborate (760 mg), and dicyclohexylmethylamine (1.87 g). The mixture is stirred at room temperature under nitrogen atmosphere for 2.5 hours, and thereto is added a saturated aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{(tert-butoxycarbonyl)-[5-(2-benzyloxycarbonylvinyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.65 g). MS (m/z): 655 $[M+H]^+$

(3) (2R,4S)-4-{(tert-Butoxycarbonyl)-[5-(2-benzyloxycarbonylvinyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.65 g) is dissolved in methylene chloride (10 ml), and thereto is added trifluoroacetic acid (1 ml). The mixture is stirred at room temperature overnight, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-[5-(2-benzyloxycarbonylvinyl)pyrimidin-2-yl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.38 g). MS (m/z): 555 $[M+H]^+$

(4) (2R,4S)-4-[5-(2-Benzyloxycarbonylvinyl)pyrimidin-2-yl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.41 g) is dissolved in N,N-dimethylformamide (30 ml), and thereto is added sodium hydride (62.7%, 360 mg) under ice-cooling. The mixture is stirred under ice-cooling for 30 minutes, and thereto is added 3,5-dibromobenzyl bromide (3 g). The mixture is stirred at room temperature

for one hour. To the reaction solution is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by chromatography (silica gel; hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[5-(2-benzyloxycarbonyl-vinyl)pyrimidin-2-yl]-(3,5-dibromobenzyl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.84 g). MS (m/z): 801/803/805 $[M+H]^+$

Example 138



The corresponding starting compound is treated in a similar manner to Example 134 to give the compound of Example 138. MS (m/z): 695 $[M+H]^+$

Examples 139-141

The corresponding starting compounds are treated in a similar manner to Example 18-(2) to give the compounds as listed in Table 20.

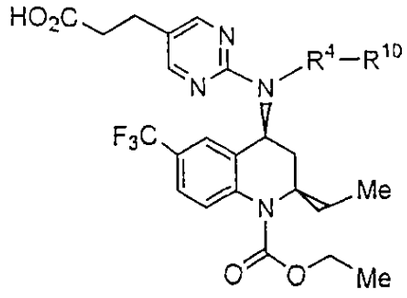
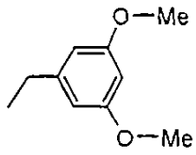
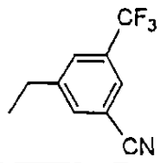
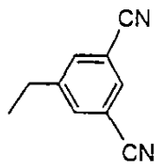


Table 20

Example	R^4-R^{10}	Physical properties, etc.
139		MS (m/z): 617 $[M+H]^+$
140		MS (m/z): 650 $[M+H]^+$
141		MS (m/z): 607 $[M+H]^+$

Example 142

(2R,4S)-4-{[5-(2-Carboxyethyl)pyrimidin-2-yl]-(3,5-dimethoxybenzyl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (145 mg) and triethylamine (98 µl) are dissolved in tetrahydrofuran (3 ml), and thereto is added dropwise ethyl chlorocarbonate (67 µl) at 0°C. The mixture is stirred at the same temperature for 30 minutes, and thereto is added sodium borohydride (44 mg). The mixture is further stirred at the same temperature for 3 hours. To the reaction solution are added an aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{(3,5-dimethoxybenzyl)-[5-(3-hydroxypropyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (68 mg). MS (m/z): 603 $[M+H]^+$

Example 143

(2R,4S)-4-[(3,5-Dimethoxybenzyl)-(5-iodopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (302 mg) is dissolved in N,N-dimethylformamide (2.5 ml), and thereto are added tetrakis(triphenylphosphine)palladium (104 mg), pyrimidine-5-boronic acid (112 mg) and sodium carbonate (114 mg). The mixture is stirred at 100°C under nitrogen atmosphere for 4 hours. The mixture is allowed to cool to room temperature, and water is added thereto. The mixture is extracted with ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by NH- silica gel column chromatography (hexane:ethyl acetate = 2:1) to give (2R,4S)-4-{[5,5']bipyrimidin-2-yl]-(3,5-dimethoxybenzyl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (106 mg). MS (m/z): 623 $[M+H]^+$

Example 144

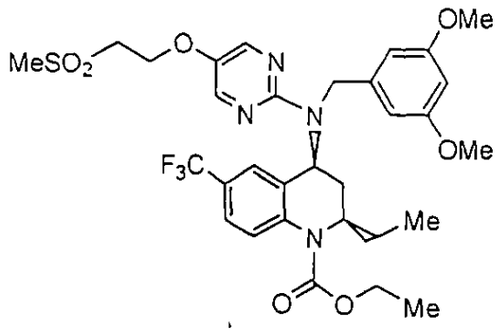
(1) (2R,4S)-4-[(3,5-Dimethoxybenzyl)-(5-iodopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.89 g) is dissolved in toluene (12 ml), and thereto are added benzyl alcohol (1.2 ml), copper(I) iodide (221 mg), cesium carbonate (1.89 g), and 1,10-phenanthroline (418 mg), and the mixture is stirred at 100°C for one day. To the reaction solution are added water and ethyl acetate, and the mixture is filtered through Celite™ to remove the insoluble materials. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is dissolved in toluene (12 ml), and thereto are added benzyl alcohol (0.3 ml), copper(I) iodide (221 mg), cesium carbonate (1.89 g), and 1,10-phenanthroline (418 mg). The mixture is stirred at 100°C for one day, and allowed to cool to room temperature. To the reaction solution are added water and ethyl acetate, and the mixture is filtered through Celite™ to

remove the insoluble materials. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-[(3,5-dimethoxybenzyl)-(5-benzyloxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.09 g). MS (m/z): 651 $[M+H]^+$

(2) (2R,4S)-4-[(3,5-Dimethoxybenzyl)-(5-benzyloxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.05 g) is dissolved in methanol (10 ml), and thereto is added 10 % palladium-carbon (1 g). The mixture is stirred at room temperature under hydrogen atmosphere for one hour. The reaction solution is filtered, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-[(3,5-dimethoxybenzyl)-(5-hydroxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.84 g). MS (m/z): 561 $[M+H]^+$

(3) (2R,4S)-4-[(3,5-Dimethoxybenzyl)-(5-hydroxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in tetrahydrofuran (2 ml), and thereto are added 2-methylsulfanylethanol (0.05 ml), triphenylphosphine (150 mg), a 40 % solution of diethyl azodicarboxylate in toluene (0.25 ml), and the mixture is stirred at room temperature for 2.5 hours. Water is added to the mixture, and the mixture is extracted with ethyl acetate The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{(3,5-dimethoxybenzyl)-[5-(2-methylsulfanylethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (224 mg). MS (m/z): 635 $[M+H]^+$

Example 145



The corresponding starting compound is treated in a similar manner to Example 50 to give the compound of Example 145. MS (m/z): 667 $[M+H]^+$

Examples 146-149

The corresponding starting compounds are treated in a similar manner to Example 96 to give the compounds as listed in Table 21.

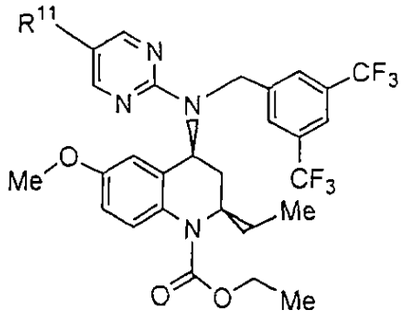
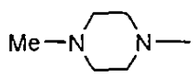
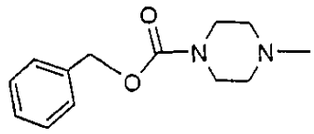
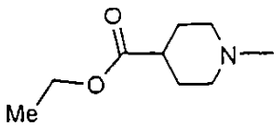
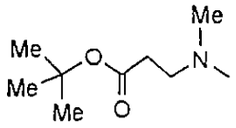


Table 21

Example	R^{11}	Physical properties, etc.
146		MS (m/z): 681 $[M+H]^+$
147		MS (m/z): 801 $[M+H]^+$

148		MS (m/z): 738 $[M+H]^+$
149		MS (m/z): 740 $[M+H]^+$

Example 150

(2R,4S)-4-{[5-(4-Benzyloxycarbonylpiperazin-1-yl)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.78 g) is dissolved in ethanol (50 ml), and thereto is added 10 % palladium-carbon (300 mg). The mixture is stirred at room temperature under hydrogen atmosphere for 3 hours. The catalyst (10 % palladium-carbon) is removed by filtration, and the filtrate is concentrated under reduced pressure, and the resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-piperazin-1-ylpyrimidin-2-yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (470 mg). MS (m/z): 667 $[M+H]^+$

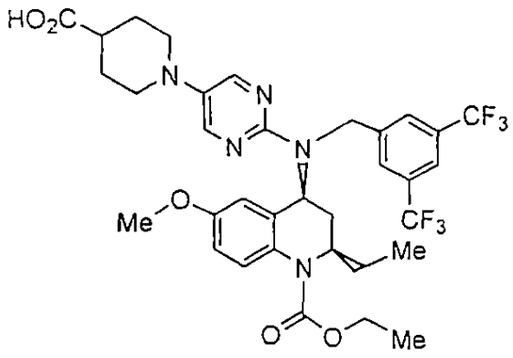
Example 151

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-piperazin-1-yl-pyrimidin-2-yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) and pyridine (18 µl) are dissolved in methylene chloride (1 ml), and thereto is added acetoxyacetic acid chloride (19.4 µl) at room temperature. The mixture is stirred overnight, and washed with a 1N hydrochloric acid. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 7:3→2:3) to give (2R,4S)-4-({5-[4-(2-acetoxyacetyl)piperazin-1-yl]pyrimidin-2-yl}-(3,5-bistrifluoromethyl-

benzyl))amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (110 mg). MS (m/z): 767 $[M+H]^+$

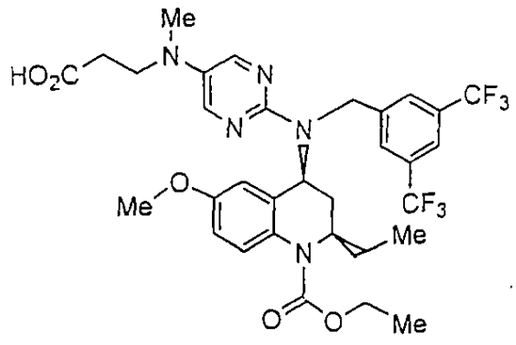
(2) (2R,4S)-4-({5-[4-(2-Acetoxyacetyl)piperazin-1-yl]pyrimidin-2-yl}-(3,5-bistrifluoromethylbenzyl))amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (87 mg) is dissolved in ethanol (1 ml), and thereto is added potassium carbonate (23 mg) at room temperature, and the mixture is stirred overnight. The insoluble materials are removed by filtration, and the filtrate is concentrated under reduced pressure to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[4-(2-hydroxyacetyl)piperazin-1-yl]pyrimidin-2-yl})amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (83 mg). MS (m/z): 725 $[M+H]^+$

Example 152



The corresponding starting compound is treated in a similar manner to Example 124 to give the compound of Example 152. MS (m/z): 710 $[M+H]^+$

Example 153



The corresponding starting compound is treated in a similar manner to Example 68 to give the compound of Example 153. MS (m/z): 684 $[M+H]^+$

Examples 154-156

The corresponding starting compounds are treated in a similar manner to Example 90 to give the compounds as listed in Table 22.

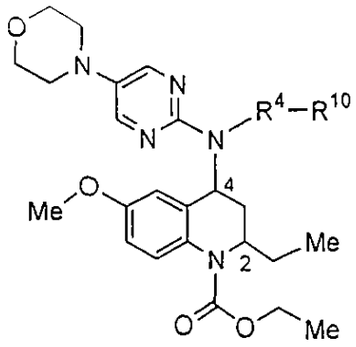
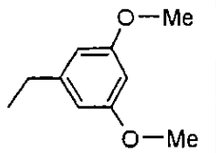
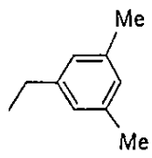
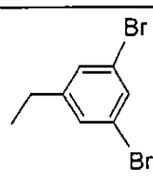
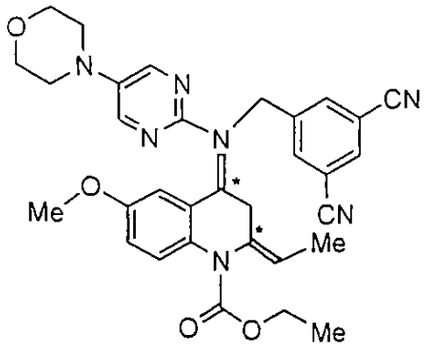


Table 22

Example	Configuration	R^4-R^{10}	Physical properties, etc.
154	(2R,4S)		MS (m/z): 592[M+H]$^-$
155	(2R,4S)		MS (m/z): 560 $[M+H]^+$
156	(2R*,4S*)		MS (m/z): 688/690/692 $[M+H]^+$

Example 157



The corresponding starting compound is treated in a similar manner to Example 134 to give the compound of Example 157. MS (m/z): 582 $[M+H]^+$

Example 158

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(6-chloropyrimidin-4-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg), an excess amount of triethylamine, and aminoacetic acid tert-butyl ester (501 mg) are dissolved in 1,3-dimethyl-imidazolidinone (4 ml), and the mixture is stirred at 90°C for 3 days. The reaction solution is cooled to room temperature, and thereto are added a saturated aqueous citric acid solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 19:1→13:7) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[6-(tert-butoxycarbonyl-methylamino)pyrimidin-4-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (22 mg). MS (m/z): 750 $[M+H]^+$

Examples 159-161

The corresponding starting compounds are treated in a similar manner to Example 158 to give the compounds as listed in Table 23

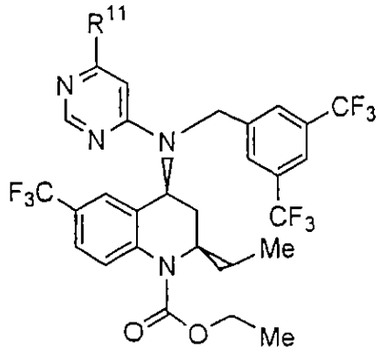
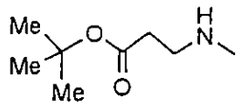
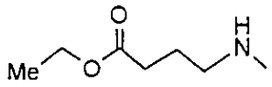
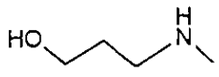


Table 23

Example	R^{11}	Physical properties, etc.
159		MS (m/z): 764 $[M+H]^-$
160		MS (m/z): 750 $[M+H]^-$
161		MS (m/z): 694 $[M+H]^-$

Example 162-163

The corresponding starting compounds are treated in a similar manner to Example 68 to give the compounds as listed in Table 24.

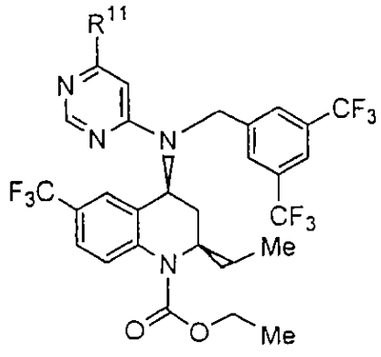
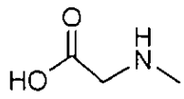
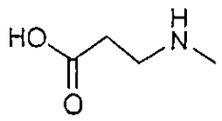
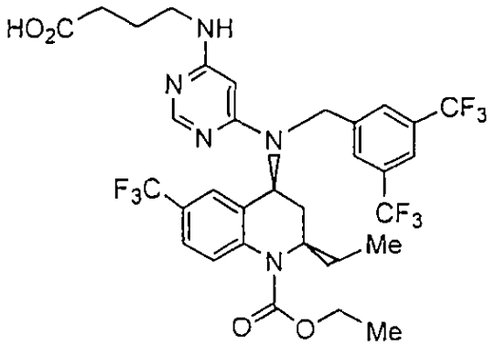


Table 24

Example	R^{11}	Physical properties, etc.
162		MS (m/z): 694 $[M+H]^+$
163		MS (m/z): 708 $[M+H]^+$

Example 164



The corresponding starting compound is treated in a similar manner to Example 124 to give the compound of Example 164. MS (m/z): 722 $[M+H]^+$

Example 165

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.5 g) and 3-bromobenzaldehyde (974 mg) are dissolved in 1,2-dichloroethane (15 ml), and thereto is added triacetoxy sodium borohydride (2.14 g) at room temperature. The mixture is stirred for 3 hours, and thereto are added an aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 19:1→7:3) to give (2R,4S)-4-(3-

bromobenzyl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.45 g). MS (m/z): 485/487 $[M+H]^+$

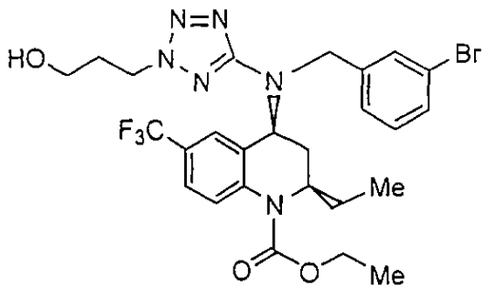
(2) (2R,4S)-4-(3-Bromobenzyl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.32 g), bromocyane (609 mg), and sodium hydrogen carbonate (1.22 g) are suspended in ethanol (30 ml), and the mixture is stirred at room temperature overnight. To the reaction solution are added an aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R,4S)-4-[cyano-(3-bromobenzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.43 g). MS (m/z): 527/529 $[M+H_2O]^+$

(3) (2R,4S)-4-[Cyano-(3-bromobenzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.43 g), sodium azide (3.12 g), and ammonium chloride (2.56 g) are dissolved in N,N-dimethylformamide (20 ml), and the mixture is stirred at 95°C overnight. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R,4S)-4-[(3-bromobenzyl)-(tetrazol-5-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.58 g). MS (m/z): 553/555 $[M+H]^+$

(4) (2R,4S)-4-[(3-Bromobenzyl)-(tetrazol-5-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg), 2-bromoethanol (271 mg), and potassium carbonate (375 mg) are dissolved in N,N-dimethylformamide (3 ml), and the mixture is stirred at 50°C overnight. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel

column chromatography (hexane:ethyl acetate = 9:1→2:3) to give (2R,4S)-4-{(3-bromobenzyl)-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (394 mg). MS (m/z): 597/599 $[M+H]^+$

Example 166



The corresponding starting compound is treated in a similar manner to Example 165-(4) to give the compound of Example 166. MS (m/z): 611/613 $[M+H]^+$

Example 167

(1) (2R,4S)-4-[(3-Bromobenzyl)-(tetrazol-5-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg), glycidol (89 µl), and triphenylphosphine (711 mg) are dissolved in tetrahydrofuran (3 ml), and thereto is added 40% azodicarboxylic acid diethyl ester in toluene (1180 mg) at room temperature, and the mixture is stirred for 15 minutes. To the reaction solution are added water and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 19:1→3:2) to give (2R,4S)-4-[(3-bromobenzyl)-(2-oxiranylmethyl-2H-tetrazol-5-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (347 mg). MS (m/z): 609/611 $[M+H]^+$

(2) (2R,4S)-4-[(3-Bromobenzyl)-(2-oxiranylmethyl-2H-tetrazol-5-yl)] amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic

acid ethyl ester (330 mg) and morpholine (1 ml) are dissolved in ethanol (3 ml), and the mixture is stirred at room temperature overnight. To the reaction solution are added water and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 2:3→0:1) to give (2R,4S)-4-{(3-bromobenzyl)-[2-(2-hydroxy-3-morpholin-4-ylpropyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (315 mg) MS (m/z): 696/698 $[M+H]^+$

Example 168

(1) (2R,4S)-4-[(3-Bromobenzyl)-(tetrazol-5-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg) is treated in a similar manner to Example 167-(1) to give (2R,4S)-4-{(3-bromobenzyl)-[2-(2-methylsulfanylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (524 mg). MS (m/z): 627/629 $[M+H]^+$

(2) (2R,4S)-4-{(3-Bromobenzyl)-[2-(2-methylsulfanylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (520 mg) is treated in a similar manner to Example 50 to give (2R,4S)-4-{(3-bromobenzyl)-[2-(2-methylsulfonylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (474 mg). MS (m/z): 659/661 $[M+H]^+$

Examples 169-172

The corresponding starting compounds are treated in a similar manner to Example 10 to give the compounds as listed in Table 25.

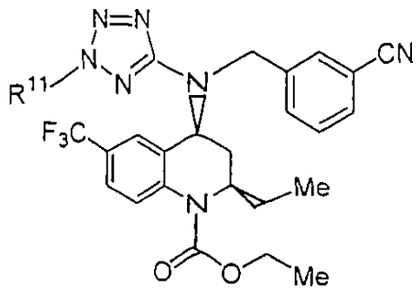
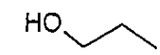
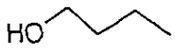
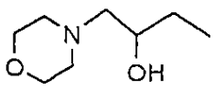
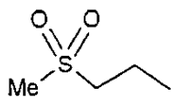


Table 25

Example	R^{11}	Physical properties, etc.
169		MS (m/z): 544 $[M+H]^+$
170		MS (m/z): 558 $[M+H]^+$
171		MS (m/z): 643 $[M+H]^+$
172		MS (m/z): 606 $[M+H]^+$

Example 173

(1) (2R*,4S*)-(4-Benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (112.8 g) is dissolved in ethanol (1000 ml), and thereto is added 10 % palladium-carbon (5.64 g), and the mixture is stirred at room temperature under hydrogen atmosphere overnight. The catalyst (10 % palladium-carbon) is removed by filtration, and filtrate is concentrated under reduced pressure. To the residue is added hexane, and the precipitated crystals are collected by filtration to give (2R*,4S*)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (70.3 g). MS (m/z): 245 $[M+H]^+$

(2) (2R*,4S*)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (70.0 g) is dissolved in tetrahydrofuran (500 ml), and thereto is added di-tert-butyl dicarbonate (68.2 g). The mixture is stirred at room

temperature overnight, and concentrated under reduced pressure. Hexane is added to the residue, and the precipitated crystals are collected by filtration to give (2R*,4S*)-4-tert-butoxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (90.7 g) MS (m/z): 345 $[M+H]^+$

(3) (2R*,4S*)-4-tert-Butoxycarbonylamino(2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (90.58 g) and triethylamine (44 ml) are dissolved in methylene chloride (900 ml), and thereto is added triphosgene (31.2 g) under ice-cooling. The reaction solution is stirred at room temperature for one hour, and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (900 ml), and thereto are added benzyl alcohol (54.4 ml), and sodium hydride (60 %, 20.2 g) under ice-cooling. The mixture is stirred at the same temperature for 3 hours. Water and ethyl acetate are added to the reaction mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is crystallized from diisopropyl ether to give (2R*,4S*)-4-tert-butoxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (104.7 g). MS (m/z): 496 $[M+H_2O]^+$

(4) (2R*,4S*)-4-tert-Butoxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (104.5 g) is dissolved in chloroform (500 ml), and thereto are added a 4N hydrochloric acid in ethyl acetate (500 ml) at room temperature. The mixture is stirred for 30 minutes, and concentrated under reduced pressure. To the residue is added diisopropyl ether, and the precipitated crystals are collected by filtration to give (2R*,4S*)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester hydrochloride (88.0 g). MS (m/z): 379 $[M+H]^+$

(5) (2R*,4S*)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester hydrochloride (25.0 g) is dissolved in a mixture of ethyl acetate and a saturated aqueous sodium hydrogen

carbonate solution, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue (23 g) and 5-bromo-2-chloropyrimidine (29.3 g) are dissolved in 1,4-dioxane (100 ml), and thereto is added N,N-diisopropylethylamine (32 ml), and the mixture is refluxed overnight. The reaction solution is cooled to room temperature, and thereto are added water and diethyl ether, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 6:1→2:1) to give (2R*,4S*)-4-(5-bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (24.0 g). MS (m/z): 535/537 $[M+H]^+$

(6) (2R*,4S*)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (13 g) is treated in a similar manner to Example 1-(2) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (20.6 g). MS (m/z): 761/763 $[M+H]^+$

(7) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (18.3 g) is treated in a similar manner to Example 1-(3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[(5-morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-3,4-dihydro-6-trifluoromethyl-2H-quinoline-1-carboxylic acid benzyl ester (11.2 g). MS (m/z): 768 $[M+H]^+$

(8) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[(5-morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (11.2 g) is treated in a similar manner to Example 150 to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[(5-morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-

dihydro-2H-quinoline (8.9 g). MS (m/z): 634 $[M+H]^+$

Example 174

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[(5-morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (500 mg) and triethylamine (132 µl) are dissolved in methylene chloride (5 ml), and thereto is added triphosgene (94 mg) at room temperature, and the mixture is stirred for one hour. The reaction solution is concentrated under reduced pressure, and the resulting residue is separated into ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (5 ml), and ethylene glycol (0.5 ml), triethylamine (295 ml) and 4-dimethylaminopyridine (26 mg) are added thereto. The mixture is stirred at room temperature overnight. The reaction solution is separated into ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 3:1→2:3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[(5-morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester (430 mg). MS (m/z): 722 $[M+H]^+$

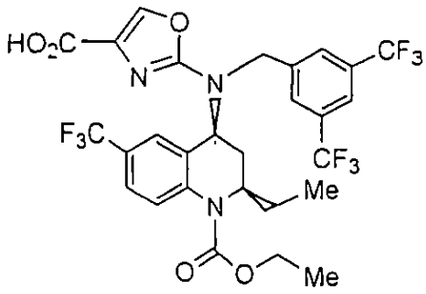
Example 175

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.28 g), 2-chloroxazole-4-carboxylic acid ethyl ester (1.44 g) and diisopropylethylamine (1.42 ml) are dissolved in 1,4-dioxane (10 ml), and the mixture is stirred at 130°C overnight. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto. The organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure.

The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-(4-ethoxycarbonyloxazol-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.13 g). MS (m/z): 456 $[M+H]^+$

(2) (2R,4S)-4-(4-Ethoxycarbonyloxazol-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.12 g) is treated in a similar manner to Example 1-(2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(4-ethoxycarbonyloxazol-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (928 mg) MS (m/z): 682 $[M+H]^+$

Example 176



The corresponding starting compound is treated in a similar manner to Example 124 to give the compound of Example 176. MS (m/z): 654 $[M+H]^+$

Example 177

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (32.25 g), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (1.012 g), potassium acetate (13.6 g), and bis(pinacolate)diboron (17.56 g) are dissolved in dimethylsulfoxide (200 ml), and the mixture is stirred at 80°C under nitrogen atmosphere for one hour. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced

pressure. The resulting residue is dissolved in tetrahydrofuran (100 ml), and thereto is added dropwise a 30 % aqueous hydrogen peroxide solution (70 ml) under ice-cooling. On hour thereafter, a saturated aqueous sodium thiosulfate solution is added to the mixture, and the excess hydrogen peroxide is consumed. The mixture is separated into water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 5:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (19.22 g). MS (m/z): 637 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (6.5 g) and 4-bromobutyric acid ethyl ester (2.19 g) are dissolved in N,N-dimethylformamide (50 ml), and thereto is added potassium carbonate (1.69 g), and the mixture is stirred at 45°C overnight. Ethyl acetate and water are added to the mixture, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (6.52 g). MS (m/z): 751 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (6.5 g) is dissolved in ethanol (65 ml), and thereto is added a 2N aqueous sodium hydroxide solution (13 ml). The mixture is stirred at room temperature overnight. The reaction solution is concentrated under reduced pressure, and to the residue are added ethyl

acetate and a 1N aqueous hydrochloric acid, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→95:5) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (6.16 g). MS (m/z): 723 $[M+H]^+$

Example 178

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) is dissolved in ethanol (3 ml), and thereto is added a 2N aqueous sodium hydroxide solution (207 µl). The reaction solution is concenrated to dryness under reduced pressure to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester sodium salt (308 mg). MS (m/z): 721 $[M-Na]^-$

Example 179

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester sodium salt (258 mg) is suspended in water (10 ml), and thereto is added a solution of calcium chloride (154 mg) in water (0.6 ml), and the mixture is stirred at room temperature overnight. Chloroform and water are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in ethyl acetate, and thereto is added n-hexane. The precipitated crystals are collected by filtration to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl

ester hemicalcium salt (169 mg). MS (m/z): 721 [M-1/2Ca]-

Example 180

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (250 mg) is dissolved in ethanol (2 ml), and thereto is added a 2N aqueous potassium hydroxide solution (173 µl). The reaction solution is concentrated to dryness under reduced pressure to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester potassium salt (266 mg). MS (m/z): 721 [M-K]-

Examples 181-186

The corresponding starting compounds are treated in a similar manner to Example 177(2) to give the compounds as listed in Table 26.

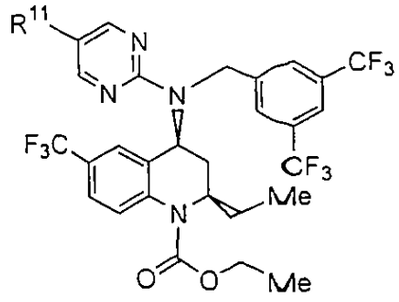
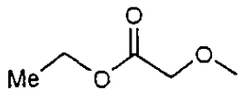
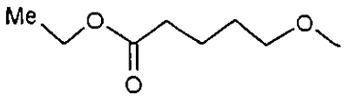
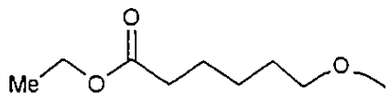
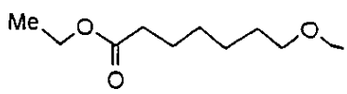
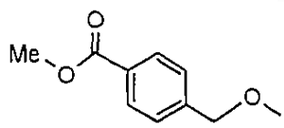
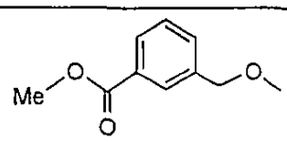


Table 26

Ex. No.	R11	Physical properties, etc.
181		MS (m/z): 723 [M+H]+
182		MS (m/z): 765 [M+H]+

183		MS (m/z): 779 [M+H]+
184		MS (m/z): 793 [M+H]+
185		MS (m/z): 785 [M+H]+
186		MS (m/z): 785 [M+H]+

Example 187

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.0 g) is dissolved in N,N-dimethylformamide (30 ml), and thereto are added ethyl bromoacetate (520 µl), potassium carbonate (650 mg). The mixture is stirred at room temperature for 3.5 hours. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 19:1→41:9) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-ethoxycarbonylmethoxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.07 g). MS (m/z): 723 [M+H]+

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-ethoxycarbonylmethoxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.07 g) is dissolved in ethanol (30 ml), and thereto is added dropwise a 1N aqueous sodium hydroxide solution. The mixture is stirred for 2.5 hours, and thereto are added a 6N

hydrochloric acid and ethyl acetate. The mixture is separated, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-carboxymethoxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.83 g). MS (m/z): 695 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-carboxymethoxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in tetrahydrofuran (4 ml), and thereto are added ethyl aminoacetate hydrochloride (48 mg), 1-hydroxybenzotriazole dihydrate (47 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimideethylene dichloride hydrochloride (66 mg), and triethylamine (49 µl), and the mixture is stirred at room temperature for one hour. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{5-[(ethoxycarbonylmethylcarbamoyl)methoxy]pyrimidin-2-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (165 mg). MS (m/z): 780 $[M+H]^+$

Examples 188-190

The corresponding starting compounds are treated in a similar manner to Example 187 (3) to give the compounds as listed in Table 27.

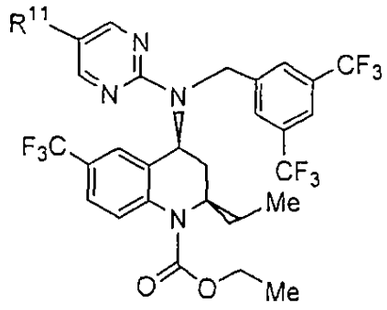
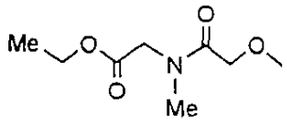
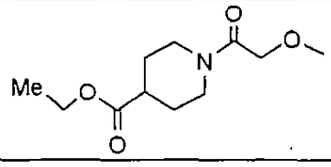
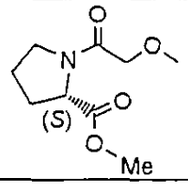


Table 27

Ex. No.	R^{11}	Physical properties, etc.
188		MS (m/z): 794 $[M+H]^+$
189		MS (m/z): 834 $[M+H]^+$
190		MS (m/z): 806 $[M+H]^+$

Example 191

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) is dissolved in tetrahydrofuran (4 ml), and thereto are added (2S,4R)-1-benzyloxycarbonyl-2-methoxycarbonyl-4-hydroxypyrrolidine (395 mg) and triphenylphosphine (740 mg). To the mixture is added dropwise a 40 % solution of diethyl azodicarboxylate in toluene (1.23 ml) under ice-cooling, and the mixture is stirred at room temperature overnight. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography

(hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[(S)-2-((S)-methoxycarbonyl)-1-benzyloxycarbonylpyrrolidin-4-yloxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (543 mg) as a crude product. MS (m/z): 898 $[M+H]^+$

(2) The crude (2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[(S)-2-((S)-methoxycarbonyl)-1-benzyloxycarbonylpyrrolidin-4-yloxy]pyrimidin-2-yl})-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.39 g) is dissolved in methanol (15 ml), and thereto is added 10 % palladium-carbon (300 mg) The mixture is stirred under hydrogen atmosphere for 3 hours, filtered, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 3:2→2:3→0:1) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[(S)-2-((S)-methoxycarbonyl)pyrrolidin-4-yl]pyrimidin-2-yloxy})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (667 mg). MS (m/z): 764 $[M+H]^+$

Example 192

(2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[(S)-2-((S)-methoxycarbonyl)pyrrolidin-4-yloxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in tetrahydrofuran (5 ml), and thereto are added acetyl chloride (44 µl) and triethylamine (88 µl) under ice-cooling. The mixture is stirred at room temperature for 4 hours, and separated into a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 3:2→2:3) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[(S)-2-((S)-methoxycarbonyl)-1-acetylpyrrolidin-4-yloxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

(212 mg). MS (m/z): 806 $[M+H]^+$

Example 193

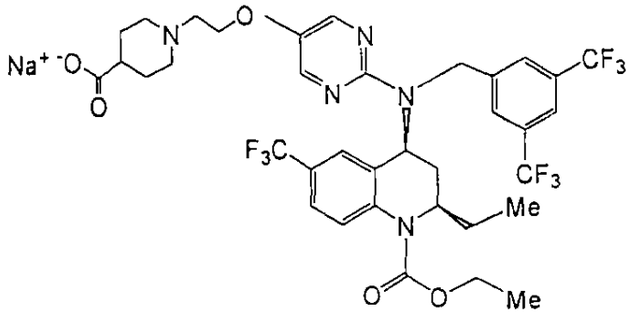
(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.5 g) is dissolved in N,N-dimethylformamide (20 ml), and thereto are added 2-bromoethanol (1.25 ml) and potassium carbonate (490 mg), and the mixture is stirred at 60°C overnight. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (493 mg). MS (m/z): 681 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (493 mg) is dissolved in methylene chloride (10 ml), and thereto are added triphenylphosphine (380 mg) and carbon tetrabromide (480 mg). The mixture is stirred at room temperature for 30 minutes, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and chloroform, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-bromoethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (298 mg). MS (m/z): 743/745 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-bromoethoxy)-

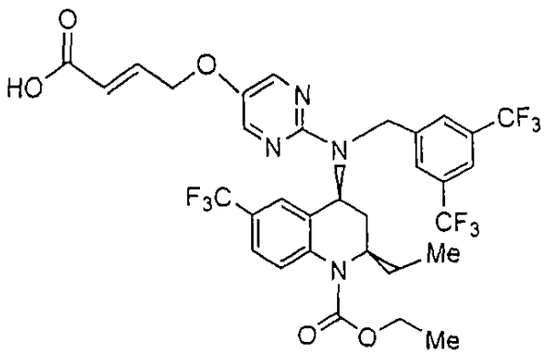
pyrimidin-2-yl}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (298 mg) is dissolved in N,N dimethylformamide (5 ml), and piperidine-4-carboxylic acid ethyl ester (185 µl) and potassium carbonate (166 mg) are added thereto, and the mixture is stirred at room temperature for 1.5 hour. The mixture is stirred at 60°C for 2.5 hours. A saturated aqueous sodium hydrogen carbonate solution and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 1:1→1:4) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[2-(4-ethoxycarbonylpiperidin-1-yl)ethoxy]pyrimidin-2-yl}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (245 mg). MS (m/z): 820 $[M+H]^+$

Example 194



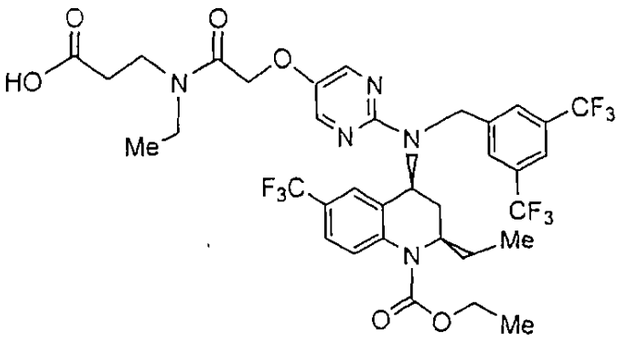
The corresponding starting compound is treated in a similar manner to Example 177 (3) and Example 178 to give the compound of Example 194. MS (m/z): 790 $[M-Na]^-$

Example 195



The corresponding starting compound is treated in a similar manner to Example 177 (2)-(3) to give the compound of Example 195. MS (m/z): 721 $[M+H]^+$

Example 196



The corresponding starting compound is treated in a similar manner to Example 187 (3) and Example 177 (3) to give the compound of Example 196. MS (m/z): 794 $[M+H]^+$

Examples 197-208

The corresponding starting compounds are treated in a similar manner to Example 177 (3) to give the compounds as listed in Table 28.

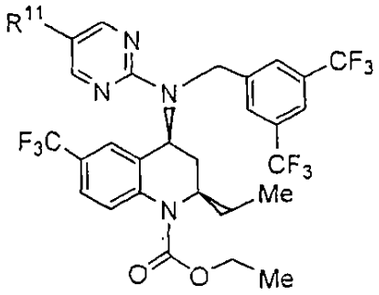
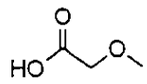
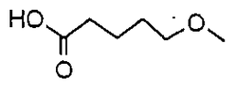
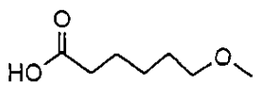
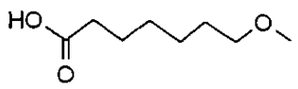
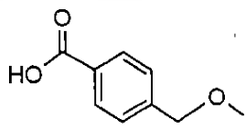
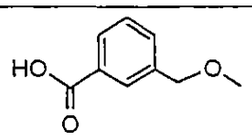
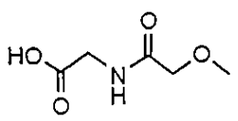
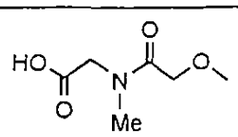
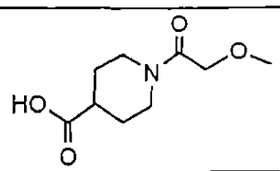
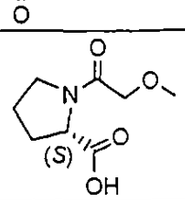
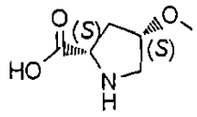
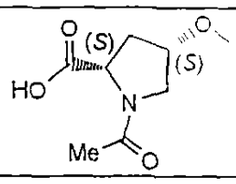


Table 28

Ex. No.	R^{11}	Physical properties, etc.
197		MS (m/z): 695 $[M+H]^+$
198		MS (m/z): 737 $[M+H]^+$
199		MS (m/z): 751 $[M+H]^+$
200		MS (m/z): 765 $[M+H]^+$
201		MS (m/z): 771 $[M+H]^+$
202		MS (m/z): 771 $[M+H]^+$
203		MS (m/z): 752 $[M+H]^+$
204		MS (m/z): 766 $[M+H]^+$
205		MS (m/z): 806 $[M+H]^+$
206		MS (m/z): 792 $[M+H]^+$

207		MS (m/z): 750 $[M+H]^+$
208		MS (m/z): 792 $[M+H]^+$

Example 209

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) is dissolved in tetrahydrofuran (3 ml), and thereto are added potassium tert-butoxide (53 mg) and β-propiolactone (30 µl) at room temperature. The reaction solution is stirred at room temperature overnight, and thereto are added ethyl acetate and 1N hydrochloric acid, and the mixture is separated. The organic layer is washed with a saturated brine, and dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in a mixture of tetrahydrofuran and methanol (5:1, 2 ml), and thereto is added a 2M solution of trimethylsilyldiazomethane in hexane (353 µl). Thirty minutes thereafter, the reaction solution is concentrated under reduced pressure, and the resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-{[3,5-bis-(trifluoromethyl)benzyl]-[5-(2-methoxycarbonylethoxy)pyrimidin-2-yl]}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (27 mg). MS (m/z): 723 $[M+H]^+$

Example 210

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (900 mg) is dissolved in tetrahydrofuran (9 ml), and thereto are added potassium tert-butoxide (158 mg) and β-propiolactone (89 µl) at room temperature. The reaction solution is stirred at room

temperature overnight, and thereto are added ethyl acetate and 1N hydrochloric acid, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-carboxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (178 mg). MS (m/z): 709 $[M+H]^+$

Example 211

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg) is dissolved in N,N-dimethylformamide (5 ml), and thereto are added 2-(2-chloroethoxy)ethanol (830 µl), and potassium carbonate (1.09 g), and the mixture stirred at room temperature for 3 hours. The reaction mixture is stirred at 60°C overnight. The reaction solution is cooled to room temperature, and the mixture is separated into water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{5-[2-(2-hydroxyethoxy)ethoxy]pyrimidin-2-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (710 mg) as a crude product. MS (m/z): 725 $[M+H]^+$

(2) The crude (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{5-[2-(2-hydroxyethoxy)ethoxy]pyrimidin-2-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (706 mg) is dissolved in methylene chloride (10 ml), and thereto is added 1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (826 mg), and the mixture is stirred at room temperature overnight. A saturated aqueous sodium hydrogen carbonate solution and ethyl acetate are added, and the mixture is

separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-formylmethoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (190 mg). MS (m/z): 723 $[M+H]^+$

Example 212

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-{5-[2-(2-oxoethoxy)-ethoxy]pyrimidin-2-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (160 mg) is dissolved in a mixture of tert-butanol (3 ml) and water (0.8 ml), and thereto are added potassium dihydrogen phosphate dihydrate (41.4 mg), sodium chlorite (85 mg), and 2-methyl-2-butene (103 µl), and the mixture is stirred at room temperature for 2 hours. To the reaction solution are added 1N hydrochloric acid and ethyl acetate under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-carboxymethoxyethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (132 mg). MS (m/z): 739 $[M+H]^+$

Example 213

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg) is dissolved in N,N-dimethylformamide (5 ml), and thereto is added 2-chloroethylcarbamic acid benzyl ester (402 mg) and potassium carbonate (260 mg), and the mixture is stirred at 80°C overnight. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is

washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[5-(2-benzyloxycarbonylaminoethoxy)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (249 mg). MS (m/z): 814 $[M+H]^+$

(2) (2R,4S)-4-{[5-(2-Benzyloxycarbonylaminoethoxy)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (240 mg) is dissolved in methanol (5 ml), and thereto is added 10 % palladium-carbon (100 mg), and the mixture is stirred under hydrogen atmosphere for 2 hours. The reaction solution is filtered and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 7:3→2:3) to give (2R,4S)-4-{[5-(2-aminoethoxy)-pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoro-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (167 mg). MS (m/z): 680 $[M+H]^+$

Example 214

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (975 mg) is dissolved in N,N-dimethylformaldehyde (4.5 ml), and thereto is added sodium hydride (62.7 %, 70 mg) under ice-cooling, and the mixture is stirred for 10 minutes. To the reaction solution is added 4-bromobutyronitrile (0.2 ml), and the mixture is stirred at room temperature for one hour. To the reaction solution are added water and ethyl acetate under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-

yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.1 g). MS (m/z): 704 $[M+H]^+$

Example 215

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg), sodium azide (462 mg), and ammonium chloride (380 mg) are dissolved in N,N-dimethylformaldehyde (1 ml), and the mixture is stirred at 120°C for 27 hours. The reaction solution is cooled to room temperature, and thereto are added 1N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-({3,5-bis(trifluoromethyl)benzyl]-{5-[3-(tetrazol-5-yl)propoxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (169 mg). MS (m/z): 747 $[M+H]^+$

Example 216

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (700 mg), hydroxylamine hydrochloride (140 mg) and sodium carbonate (212 mg) are dissolved in ethanol (3 ml), and the mixture is refluxed for 41 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give (2R,4S)-4-({3,5-bis(trifluoromethyl)benzyl]-{5-[3-(N-hydroxycarbamimidoyl)propoxy]pyrimidin-2-yl})-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (502 mg). MS (m/z): 737 $[M+H]^+$

Example 217

(2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[3-(N-hydroxy-carbamimidoyl)propoxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg), and 1,1'-carbonyldiimidazole (66 mg) are dissolved in acetonitrile (1.5 ml), and the mixture is stirred at 60°C for 16.5 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[3-(5-oxo-4,5-dihydro[1,2,4]oxadiazol-3-yl)propoxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (115 mg). MS (m/z): 763 $[M+H]^+$

Example 218

(2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[3-(N-hydroxy-carbamimidoyl)propoxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (240 mg) and pyridine (106 µl) are dissolved in tetrahydrofuran (7.5 ml), and thereto is added dropwise a solution of thionyl chloride (48 µl) in methylene chloride (3 ml), and the mixture is stirred for 2 hours and 40 minutes. The reaction solution is concentrated under reduced pressure, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[3-(2-oxo-3H-[1,2,3,5]-oxothiazol-4-yl)propoxy]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (181 mg). MS (m/z): 783 $[M+H]^+$

Example 219

3-Chloropropane-1-sulfonyl chloride (0.38 ml) is dissolved in methylene chloride (15 ml), and ammonia gas is blown into the mixture for 15 minutes. The reaction solution is stirred overnight, and the resulting ammonium chloride is removed by filtration. The filtrate is concentrated, and the resulting 3-chloropropane-1-sulfonamide and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg), potassium iodide (1.3 g), and potassium hydroxide (352 mg) are dissolved in dimethylsulfoxide (4 ml), and the mixture is stirred at 60°C for 24 hours. The mixture is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-sulfamoylpropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (22 mg). MS (m/z): 758 $[M+H]^+$

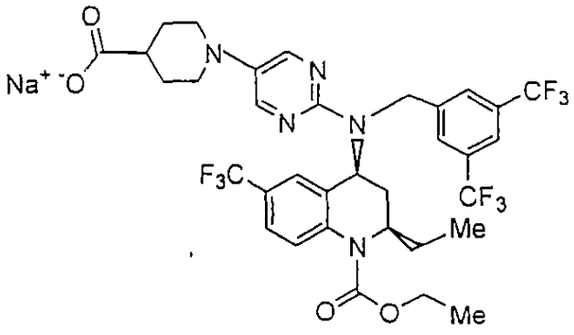
Example 220

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) is dissolved in tetrahydrofuran (5 ml), and thereto are added ethy 4-(hydroxymethyl)cyclohexylacetate (141 mg) and triphenylphosphine (370 mg) To the mixture is added dropwise a 40 % solution of diethyl azodicarboxylate in toluene (600 µl) under ice-cooling, and the mixture is stirred at room temperature for 2.5 hours. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate =

19:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonylmethylcyclohexylmethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (275 mg). MS (m/z): 819 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonylmethylcyclohexylmethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (220 mg) is dissolved in ethanol (5 ml), and thereto is added dropwise a 1N aqueous sodium hydroxide solution (1 ml), and the mixture is stirred at room temperature overnight. To the mixture are added 1N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-carboxymethylcyclohexylmethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (181 mg). MS (m/z): 791 $[M+H]^+$

Example 221



The corresponding starting compound is treated in a similar manner to Example 178 to give the compound of Example 221. MS (m/z): 746 [M-Na]$^-$

Examples 222-224

The corresponding starting compounds are treated in a similar

manner to Example 1(3) to give the compounds as listed in Table 29.

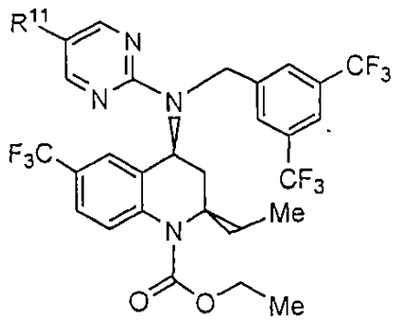
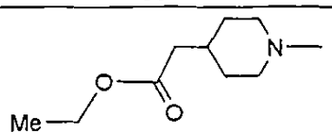
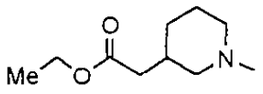
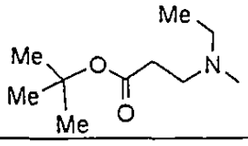


Table 29

Ex. No.	R^{11}	Physical properties, etc.
222		MS (m/z): 790 $[M+H]^+$
223		MS (m/z): 790 $[M+H]^+$
224		MS (m/z): 792 $[M+H]^+$

Examples 225-226

The corresponding starting compounds are treated in a similar manner to Example 177 (3) to give the compounds as listed in Table 30.

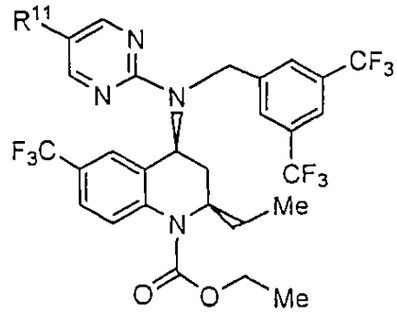
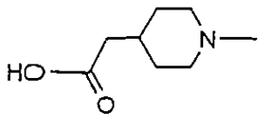
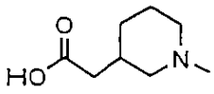


Table 30

Ex. No.	R^{11}	Physical properties, etc.
225		MS (m/z): 762[M+H]+
226		MS (m/z): 762[M+H]+

Example 227

(2R,4S)-4-[[3,5-Bis(trifluoromethyl)benzyl]-(5-{[ethyl-(2-tert-butoxy-carbonylethyl)]amino}pyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (70 mg) is dissolved in a 4N hydrogen chloride in ethyl acetate (0.5 ml), and the mixture is stirred at room temperature for 3 hours. To the reaction solution are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure to give (2R,4S)-4-[[3.5-bis(trifluoromethyl)benzyl]-(5-{[ethyl-(2-carboxyethyl)]amino}pyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (65 mg). MS (m/z): 736 $[M+H]^+$

Example 228

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-iodopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.0 g), copper iodide (13 mg), potassium carbonate (370 mg), ethylene glycol (0.15 ml), and 4-mercaptobutanol (0.14 ml) are dissolved in isopropyl alcohol (1.5 ml), and the mixture is stirred at 80°C under nitrogen atmosphere for 15 hours. The mixture is cooled to room temperature, and thereto is added ethyl acetate. The insoluble materials

are removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfanyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (705 mg). MS (m/z): 725 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfanyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg) is dissolved in chloroform (2 ml), and thereto is added m-chloroperbenzoic acid (75 %, 636 mg) under ice-cooling. The mixture is stirred at room temperature for one hour, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 7:3—1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfonyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (309 mg). MS (m/z): 757 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfonyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) and 1,1,1,tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (269 mg) are dissolved in methylene chloride (2 ml), and the mixture is stirred for 2.5 hours. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropylsulfonyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-

2H-quinoline-1-carboxylic acid ethyl ester (103 mg). MS (m/z): 771 [M+H]+

Example 229

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3 g), 2-chloro-4-methylthiazole-5-carboxylic acid ethyl ester (5.85 g) and diisopropylethylamine (3.3 ml) are dissolved in 1,4-dioxane (25 ml), and the mixture is stirred at 130°C for one week. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 6:1→4:1) to give (2R,4S)-4-(5-ethoxycarbonyl-4-methylthiazol-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.93 g). MS (m/z): 486 [M+H]+

(2) (2R,4S)-4-(5-Ethoxycarbonyl-4-methylthiazol-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.9 g) is dissolved in N,N-dimethylformamide (20 ml), and thereto is added sodium hydride (62.7 %, 282 mg) under ice-cooling. The reaction mixture is stirred at room temperature for 30 minutes, and thereto is added 3,5-bis(trifluoromethyl)benzyl bromide (1.56 ml) under ice-cooling. The mixture is stirred at room temperature for 3 hours, and a saturated aqueous citric acid solution and ethyl acetate are added thereto, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9.1→4.1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-ethoxycarbonyl-4-methylthiazol-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.62 g) MS (m/z): 712 [M+H]+

Example 230

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-ethoxycarbonyl-4-methylthiazol-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (250 mg) and lithium hydroxide monohydrate (147 mg) are dissolved in a mixture of ethanol (5 ml) and a 2N aqueous sodium hydroxide solution (703 µl), and the mixture is stirred at 70°C for 2 hours. The reaction solution is cooled to room temperature, and acidified with a 2N aqueous hydrochloric acid. Subsequently, to the mixture is added ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-carboxy-4-methylthiazol-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (189 mg). MS (m/z): 684 $[M+H]^+$

Example 231

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (10.0 g), 2,5-dibromopyridine (15 g), tris(dibenzylideneacetone)dipalladium (2.9 g), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (2.5 g) and sodium tert-butoxide (6.1 g) are dissolved in toluene (100 ml), and the mixture is stirred at 80°C for 15 hours under nitrogen atmosphere. The mixture is cooled to room temperature, and water and ethyl acetate are added thereto, and the mixture is separated. The organic layer is washed with water and a saturated brine, and thereto is added NH-silica gel, and the mixture is filtered. The filtrate is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-(5-bromopyridin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.56 g). MS (m/z): 472/474 $[M+H]^+$

(2) (2R,4S)-4-(5-Bromopyridin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-

dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.4 g) is dissolved in N,N-dimethylformamide (15 ml), and thereto is added sodium hydride (40 %, 335 mg) under ice-cooling. The mixture is stirred at room temperature for 30 minutes, and thereto is added 3,5-bis(trifluoromethyl-benzyl bromide (1.1 ml). The mixture is stirred at room temperature for 5 hours. To the mixture are added water and diethyl ether under ice-cooling, and the mixture is separated. The organic layer is washed with 1N hydrochloric acid, water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3.5-bis(trifluoromethyl)benzyl]-(5-bromopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.72 g). MS (m/z): 698/700 $[M+H]^+$

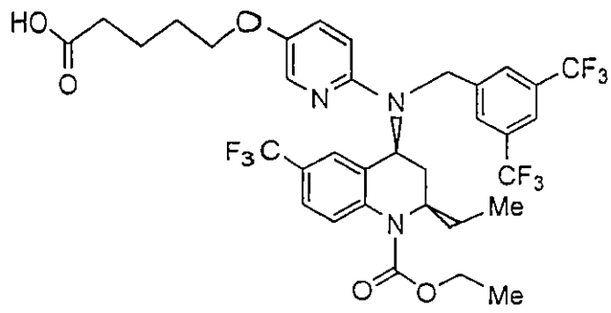
(3) (2R,4S)-4-{[3.5-Bis(trifluoromethyl)benzyl]-(5-bromopyridin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.72 g), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (54 mg), potassium acetate (725 mg) and bis(pinacolate)diboron (938 mg) are dissolved in deaerated dimethylsulfoxide (7 ml), and the mixture is stirred at 80°C for one hour. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (7.5 ml), and thereto is added a 30 % aqueous hydrogen peroxide solution (2.8 ml) under ice-cooling, and the mixture is stirred for 3 hours. A saturated aqueous sodium thiosulfate solution and ethyl acetate are added to the mixture under ice-cooling, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate =

4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (851 mg). MS (m/z): 636 $[M+H]^+$

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in N,N-dimethylformamide (1.5 ml), and thereto is added sodium hydride (15 mg) under ice-cooling. The mixture is stirred for 15 minutes, and thereto is added 4-bromobutyric acid ethyl ester (69 µl), and the mixture is stirred at room temperature for 1.5 hour. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (132 mg). MS (m/z): 750 $[M+H]^+$

(5) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (120 mg) is dissolved in ethanol (0.8 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.24 ml), and the mixture is stirred for 3 hours. To the reaction solution are added a 2N hydrochloric acid solution (0.24 ml) and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (105 mg). MS (m/z): 722 $[M+H]^+$

Example 232



The corresponding starting compound is treated in a similar manner to Example 231 (4)-(5) to give the compound of Example 232. MS (m/z): 736 $[M+H]^+$

Example 233

(1) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (18 g) is dissolved in tetrahydrofuran (180 ml), and thereto are added di-tert-butyl dicarbonate (24.8 g) and a catalytic amount of dimethylaminopyridine, and the mixture is stired at room temperature overnight. To the mixture are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 8:1) to give (2R,4S)-4-[(5-bromopyrimidin-2-yl)-tert-butoxycarbonyl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (22.5 g). MS (m/z): 573/575 $[M+H]^+$

(2) (2R,4S)-4-[(5-Bromopyrimidin-2-yl)-tert-butoxycarbonyl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (22.5 g) is dissolved in 1,4-dioxane (110 ml), and thereto are added copper (I) iodide (375 mg), sodium iodide (11.8 g) and N,N'-dimethylethane-1,2-diamine (0.42 ml), and the mixture is refluxed under nitrogen atmosphere overnight. The reaction solution is cooled to room temperature,

and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give (2R,4S)-4-[tert-butoxycarbonyl-(5-iodopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (21.6 g). MS (m/z): 621 $[M+H]^+$

(3) (2R,4S)-4-[tert-Butoxycarbonyl-(5-iodopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.0 g), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (35 mg), potassium acetate (475 mg) and bis(pinacolate)diboron (615 mg) are dissolved in deaerated dimethylsulfoxide (8 ml), and the mixture is stirred at 80°C for 18 hours. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (8 ml), and thereto is added an excess amount of a 30 % aqueous hydrogen peroxide solution under ice-cooling, and the mixture is stirred for 6 hours. A saturated aqueous sodium thiosulfate solution and ethyl acetate are added to the mixture under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→19:1) to give (2R,4S)-4-[tert-butoxycarbonyl-(5-hydroxypyrimidin-2-yl)] amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.7 g). MS (m/z): 511 $[M+H]^+$

(4) (2R,4S)-4-[tert-Butoxycarbonyl-(5-hydroxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (800 mg) is dissolved in N,N-dimethylformamide (5 ml), and thereto is

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added sodium hydride (62.7 %, 72 mg) under ice-cooling. The mixture is stirred at room temperature for 15 minutes, and thereto is added 1-chloro-2-methylsulfanylethane (259 mg), and the mixture is stirred at room temperature for 24 hours. Water and ethyl acetate are added to the reaction mixture under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:7) to give (2R,4S)-4-{tert-butoxycarbonyl-[5-(2-methylsulfanyl-ethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg). MS (m/z): 585 $[M+H]^+$

(5) (2R,4S)-4-{tert-Butoxycarbonyl-[5-(2-methylsulfanylethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in a 4N hydrogen chloride in 1,4-dioxane (1.5 ml), and the mixture is stirred at room temperature for 17.5 hours. To the reaction solution are added a 2N aqueous sodium hydroxide solution (3 ml) and diethyl ether, and the mixture is separated. The organic layer is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-2-ethyl-4-[5-(2-methylsulfanylethoxy)pyrimidin-2-yl]amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (170 mg) MS (m/z): 485 $[M+H]^+$

(6) (2R,4S)-2-Ethyl-4-[5-(2-methylsulfanylethoxy)pyrimidin-2-yl]amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (160 mg) is dissolved in N,N-dimethylformamide (1.5 ml), and thereto is added sodium hydride (62.7 %, 15 mg) under ice-cooling. The mixture is stirred at room temperature for 30 minutes, and thereto is added 3,5-dibromobenzyl bromide (141 mg), and the mixture is stirred at room temperature for 19 hours. To the mixture is added a 0.5N hydrochloric

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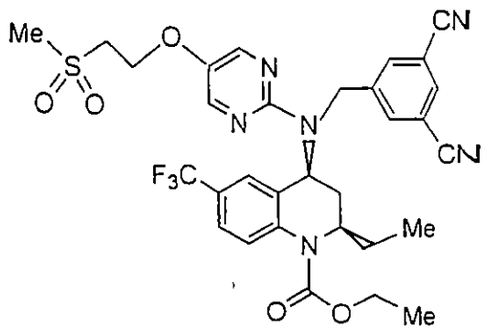
acid and diethyl ether under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{(3,5-dibromobenzyl)-[5-(2-methylsulfanyl-ethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (110 mg) MS (m/z): 733 $[M+H]^+$

(7) (2R,4S)-4-{(3,5-Dibromobenzyl)-[5-(2-methylsulfanylethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) is dissolved in N,N-dimethyl-formamide (2 ml), and thereto are added zinc cyanide (35.3 mg) and a catalytic amount of tetrakis(triphenylphosphine)palladium, and the mixture is stirred at 110°C for 17.5 hours. The reaction solution is cooled to room temperature, and water and diethyl ether are added thereto, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{(3-bromo-5-cyanobenzyl)-[5-(2-methylsulfanylethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (28 mg, MS (m/z): 678/680 $[M+H]^+$), and (2R,4S)-4-{(3,5-dicyanobenzyl)-[5-(2-methylsulfanylethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (50 mg, MS (m/z): 625 $[M+H]^+$).

(8) (2R,4S)-4-{(3-Bromo-5-cyanobenzyl)-[5-(2-methylsulfanylethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (25 mg) is dissolved in chloroform (0.5 ml), and thereto is added m-chloroperbenzoic acid (75 %, 17 mg), and the mixture is stirred at room temperature for 35 minutes. A saturated aqueous sodium hydrogen carbonate solution and ethyl acetate are added

to the mixture, and the mixture is separated. The organic layer is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give (2R,4S)-4-{(3-bromo-5-cyanobenzyl)-[5-(2-methylsulfonylethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (29 mg). MS (m/z): 710/712 $[M+H]^+$

Example 234



The corresponding starting compound is treated in a similar manner to Example 233 (8) to give the compound of Example 234. MS (m/z): 657 $[M+H]^+$

Example 235

(1) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.0 g) is dissolved in N,N-dimethylformamide (10 ml), and thereto is added sodium hydride (62.7 %, 89 mg) under ice-cooling. The mixture is stirred at room temperature for 15 minutes, and thereto are added 3-cyano-5-trifluoromethylbenzyl bromide (669 mg), and the mixture is stirred at room temperature for 20 hours. Water and diethyl ether are added to the mixture, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-[(5-bromopyrimidin-2-yl)-(3-cyano-5-trifluoromethylbenzyl)]-

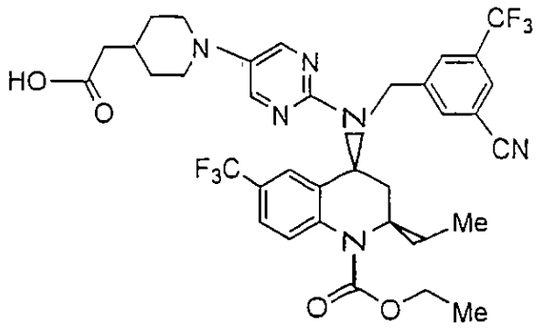
amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.08 g) MS (m/z): 656/658 [M+H]+

(2) (2R,4S)-4-[(5-Bromopyrimidin-2-yl)-(3-cyano-5-trifluoromethyl-benzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (250 mg), tris(dibenzylideneacetone)dipalladium (35 mg), 2-(di-tert-butylphosphino)diphenyl (45 mg), sodium tert-butoxide (55 mg), and piperidine-4-carboxylic acid ethyl ester (88 µl) are dissolved in toluene (2 ml), and the mixture is stirred at room temperature for 2.5 hours. The reaction solution is stirred at 80°C for 15 hours. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washd with a saturated aqueous sodium hydrogen carbonate solution and water, a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{(3-cyano-5-trifluoromethylbenzyl)-[5-(4-ethoxycarbonylpiperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (126.8 mg). MS (m/z): 733 [M+H]+

(3) (2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (120 mg) is dissolved in ethanol (4 ml), and thereto is added 2N aqueous sodium hydroxide solution (1 ml), and the mixture is stirred at room temperature for 3 hours. To the mixture are added 2N hydrochloric acid (1 ml) and ethyl acetate, and the mixture is separated. The organic layer is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) and by LC/MS (CAPCEL PAK MG II (Shiseido Co., Ltd.), water:methanol = 60:40→methanol, 40 ml/min) to give (2R,4S)-4-{[5-(4-carboxypiperidin-1-yl)pyrimidin-2-yl]-(3-cyano-5-trifluoromethylbenzyl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-

quinoline-1-carboxylic acid ethyl ester (18.6 mg). MS (m/z) 719 $[M+H]^+$

Example 236



The corresponding starting compound is treated in a similar manner to Example 235 (2)-(3) to give the compound of Example 236. MS (m/z): 719 $[M+H]^+$

Example 237

(1) (2R,4S)-4-[(5-Bromopyrimidin-2-yl)-(3-cyano-5-trifluoromethyl-benzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (10 g), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (395 mg), potassium acetate (5.3 g) and bis(pinacolate)-diboron (6.8 g) are dissolved in deaerated dimethylsulfoxide (50 ml), and the mixture is stirred at 80°C for 30 minutes. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (50 ml), and thereto is added a 30 % aqueous hydrogen peroxide solution (9 ml) under ice-cooling, and the mixture is stirred for 16 hours. A saturated aqueous sodium thiosulfate solution and ethyl acetate are added to the mixture under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate =

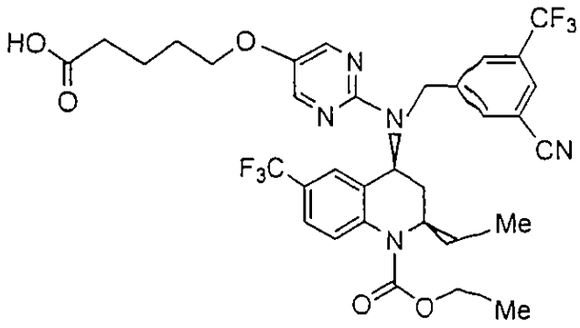
9:1→7:3) to give (2R,4S)-4-[(3-cyano-5-trifluoromethylbenzyl)-(5-hydroxy-pyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (7.7 g). MS (m/z): 594 $[M+H]^+$

(2) (2R,4S)-4-[(3-Cyano-5-trifluoromethylbenzyl)-(5-hydroxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg) is dissolved in N,N-dimethylformamide (2.5 ml), and sodium hydride (62.7 %, 119 mg) is added thereto under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. To the reaction solution is added 4-bromobutyric acid ethyl ester (185 µl), and the mixture is stirred at room temperature for 17 hours. To the reaction solution are added water and ethyl acetate under ice-cooling, and the mixture is separated. The organic layer is washed with 1N hydrochloric acid, water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{(3-cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (380 mg). MS (m/z): 708 $[M+H]^+$

(3) (2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (37 0 mg) is dissolved in a mixture of ethanol (1.5 ml) and tetrahydrofuran (1 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.79 ml), and the mixture is stirred at room temperature for 3 hours. To the reaction solution is added a 2N hydrochloric acid (0.8 ml), and the mixture is concentrated under reduced pressure. To the resulting residue are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromato-

graphy (hexane:ethyl acetate = 9:1→7:3), and LC/MS (CAPCEL PAK MG II (Shiseido Co. Ltd.), water:methanol = 50:50→methanol, 40 ml/min) to give (2R,4S)-4-{[5-(3-carboxypropoxy)pyrimidin-2-yl]-(3-cyano-5-trifluoromethylbenzyl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (167 mg). MS (m/z): 680 $[M+H]^+$

Example 238



The corresponding starting compound is treated in a similar manner to Example 237 (2)-(3) to give the compound of Example 238. MS (m/z): 694 $[M+H]^+$

Example 239

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (330 mg) is dissolved in dimethylsulfoxide (2.5 ml), and thereto are added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (11 mg), potassium acetate (147 mg) and bis(pinacolate)diboron (190 mg), and the mixture is stirred at 80°C under nitrogen atmosphere for one hour. The reaction solution is cooled to room temperature, and thereto are added a saturated brine and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (3 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.3 ml), and further thereto is added dropwise a 30 % aqueous hydrogen peroxide solution (3 ml) under ice-cooling. The

mixture is stirred at room temperature for one hour, and a saturated aqueous sodium thiosulfate solution is added thereto under ice-cooling. Then, a 10 % aqueous citric acid solution and ethyl acetate are added to the mixture, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (144 mg). MS (m/z): 599 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (141 mg) is dissolved in N,N-dimethylformamide (1.5 ml), and thereto are added potassium carbonate (65 mg) and 4-bromobutyric acid ethyl ester (44 µl). The mixture is stirred at room temperature overnight. A saturated brine and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate =4:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (141 mg). MS (m/z): 713 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (137 mg) is dissolved in 1,4-dioxane (1 ml), and thereto is added a 2N aqueous sodium hydroxide solution (1 ml), and the mixture is stirred at 40°C for one hour. The reaction solution is cooled to room temperature, and acidified with a 10 % aqueous citric acid solution. Subsequently, ethyl acetate is added to the mixture, and the

organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl) benzyl]-[5-(3-carboxy-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (123 mg). MS (m/z): 685 $[M+H]^+$

Example 240

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.28 g) is dissolved in tetrahydrofuran (7 ml), and thereto is added sodium hydride (63 %, 107 mg) under ice-cooling, and the mixture is stirred at 0°C under nitrogen atmosphere for 30 minutes. To the reaction mixture is added chloromethyl methyl ether (0.40 ml) under ice-cooling, and the mixture is stirred at room temperature for one hour. A saturated aqueous sodium hydrogen carbonate solution and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 10:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-methoxymethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.95 g). MS (m/z): 693/691 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-methoxymethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.93 g) is dissolved in dimethylsulfoxide (8 ml), and the mixture is deaerated. To the mixture are added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (61 mg), potassium acetate (822 mg) and bis(pinacolate)diboron (1.06 g), and the mixture is stirred at 80°C under nitrogen atmosphere for 45 minutes. The reaction solution is cooled to room temperature, and thereto are added a saturated brine and ethyl

acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (24 ml), and thereto is added a 2N aqueous sodium hydroxide solution (14 ml), and further added dropwise a 30 % aqueous hydrogen peroxide solution (10 ml) under ice-cooling. The mixture is stirred at the same temperature for 30 minutes, and thereto is added a saturated aqueous sodium thiosulfate solution under ice-cooling, and further thereto are added a 10 % aqueous citric acid solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1—3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-methoxymethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.49 g). MS (m/z): 629 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-methoxymethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.49 mg) is dissolved in N,N-dimethylformamide (7 mL), and thereto is added sodium hydride (62.7 %, 109 mg) under ice-cooling, and the mixture is stirred at room temperature for 40 minutes. To the reaction solution is added 4-bromobutyric acid ethyl ester (0.52 mL), and the mixture is stirred at room temperature for 3 hours. To the reaction solution are added water and ethyl acetate-hexane = 4:1 under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-methoxymethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.29 g). MS (m/z): 743 $[M+H]^+$

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-methoxymethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.29 g) is dissolved in tetrahydrofuran (5.2 mL), and thereto is added a 6N hydrochloric acid (0.58 mL) under ice-cooling, and the mixture is stirred at 50°C for 2.5 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→7:3→chloroform:methanol = 9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (614 mg, MS (m/z): 699 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (550 mg, MS (m/z): 671 $[M+H]^+$).

(5) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (610 mg), and pyridine (424 µl) are dissolved in methylene chloride (4 mL), and thereto is added dropwise trifluoromethanesulfonic anhydride (354 µl) under ice-cooling. The reaction solution is stirred for 3.5 hours, and thereto are added a saturated aqueous citric acid solution and diethyl ether, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethanesulfonyloxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (555 mg). MS (m/z): 831 $[M+H]^+$

(6) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethane sulfonyloxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (220 mg), dimethylamine (a 2N tetrahydrofuran solution, 0.16 mL), palladium acetate (0.6 mg), 2-(di-tert-butylphosphino)diphenyl (3.3 mg) and sodium tert-butoxide (36 mg) are dissolved in toluene (0.52 mL), and the mixture is stirred at 80°C for 21 hours under nitrogen atmosphere in a sealed vessel. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-6-dimethylamino-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (53 mg). MS (m/z): 726 $[M+H]^+$

(7) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-6-dimethylamino-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (48 mg) is dissolved in ethanol (0.3 mL), and thereto is added a 2N aqueous sodium hydroxide solution (0.1 mL), and the mixture is stirred at room temperature for 30 minutes. To the reaction solution are added a saturated aqueous citric acid solution and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-6-dimethylamino-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (29 mg). MS (m/z): 698 $[M+H]^+$

Example 241

(1) (2R*,4S*)-4-Benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-

1,2,3,4-tetrahydroquinoline (112.8 g) is dissolved in methanol (1000 ml) and thereto is added 10 % palladium-carbon (5.64 g), and the mixture is stirred at room temperature under hydrogen atmosphere overnight. The palladium carbon is removed by filtration, and the filtrate is concentrated under reduced pressure. To the resulting residue is added n-hexane, and the precipitated crystals are collected by filtration and washed to give (2R*,4S*)-(4-amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (70.3 g). MS (m/z): 245 $[M+H]^+$

(2) (2R*,4S*)-(4-Amino-2-ethyl-6-trifluoromethyl-1,2.3,4-tetrahydroquinoline (70 g) and di-tert-butyl dicarbonate (68.2 g) are dissolved in tetrahydrofuran (500 ml), and the mixture is stirred at room temperature overnight. The reaction solution is concentrated under reduced pressure, and thereto is added n-hexane. The precipitated crystals are collected by filtration to give (2R*,4S*)-4-tert-butoxycarbonylamino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinoline (90.7 g). MS (m/z): 345 $[M+H]^+$

(3) (2R*,4S*)-4-tert-Butoxycarbonylamino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (90.58 g) and triethylamine (44 ml) are dissolved in methylene chloride (900 ml), and thereto is added triphosgene (31.2 g) under ice-cooling, and the mixture is stirred at room temperature for one hour. The reaction solution is concentrated under reduced pressure, and the resulting residue and benzyl alcohol (54.4 ml) are dissolved in tetrahydrofuran (900 ml), and thereto is added sodium hydride (20.2 g) under ice-cooling, and the mixture is stirred at the same temperature for 3 hours. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is crystallized from isopropyl ether to give (2R*,4S*)-4-tert-butoxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (104.7 g). MS (m/z):

496 $[M+ H_2O]^+$

(4) (2R*,4S*)-4-tert-Butoxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (104.5 g) is dissolved in chloroform (500 ml), and thereto is added a 4N hydrochloric acid in ethyl acetate (500 ml), and the mixture is stirred at room temperature for 30 minutes. The reaction solution is concentrated under reduced pressure, and to the resulting residue is added isopropyl ether, and the precipitated crystals are collected by filtration and washed to give (2R*,4S*)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester hydrochloride (88.0 g). MS (m/z): 379 $[M-HCl]^+$

(5) (2R*,4S*)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester hydrochloride (12 g) is dissolved in a mixture of a 2N aqueous sodium hydroxide solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue, and 5-bromo-2-chloropyrimidine (16.8 g) and diisopropylethylamine (15 ml) are dissolved in 1,4-dioxane (100 ml), and the mixture is stirred at 130°C for 24 hours. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R*,4S*)-4-(5-bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (9.39 g) MS (m/z): 535/537 $[M+H]^+$

(6) (2R*,4S*)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (5 g), tris(dibenzylideneacetone)dipalladium (1.71 g), sodium tert-butoxide (1.35 g), 2-(di-tert-butylphosphino)biphenyl (2.22 g), and morpholine (1.22 ml)

are dissolved in toluene (50 ml), and the mixture is stirred at 50°C under nitrogen atmosphere for 5 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 2:1→1:1), then by NH-silica gel column chromatography (hexane:ethyl acetate = 2:1→1:1) to give (2R*,4S*)-2-ethyl-4-[5-(morpholin-4-yl)pyrimidin-2-yl]amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.58 g). MS (m/z): 542 $[M+H]^+$

(7) (2R*,4S*)-2-Ethyl-4-[5-(morpholin-4-yl)pyrimidin-2-yl]amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.57 g) is dissolved in N,N-dimethylformamide (20 ml), and thereto is added sodium hydride (62.7 %, 257 mg) under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. To the mixture is added 3,5-dibromobenzyl bromide (2.64 g) under ice-cooling, and the mixture is stirred at room temperature overnight. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 6:1→4:1) to give (2R*,4S*)-4-{(3,5-dibromobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.41 g). MS (m/z): 788/780 $[M+H]^+$

(8) (2R*,4S*)-4-{(3,5-Dibromobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.38 g), a catalytic amount of tetrakis(triphenylphosphine)palladium and zinc cyanide (779 mg) are dissolved in N,N-dimethylformamide (40 ml), and the mixture is stirred at 110°C under nitrogen atmosphere for 4 hours. The reaction solution is cooled to room

temperature, and thereto are added water and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→2:1) to give (2R*,4S*)-4-{(3,5-dicyanobenzyl)-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.66 g). MS (m/z): 682 $[M+H]^+$

Example 242

(1) (2R*,4S*)-4-{(3,5-Dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.6 g) is dissolved in a mixture of methanol (10 ml) and tetrahydrofuran (10 ml), and thereto is added a catalytic amount of 10 % palladuim-carbon, and the mixture is stirred at room temperature under hydrogen atmosphere for one hour. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 2:1→1:1) to give (2R*,4S*)-4-{(3,5-dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1.07 g). MS (m/z): 548 $[M+H]^+$

(2) (2R*,4S*)-4-{(3,5-Dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}-amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (150 mg) and triethylamine (76 µl) are dissolved in dichloromethane (1.5 ml), and thereto is added triphosgene (33 mg) under ice-cooling, and the mixture is stirred at room temperature for 3 hours. To the reaction solution are added water and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue and ethylene glycol (1 ml) are dissolved in tetrahydrofuran (2.5 ml), and thereto are added triethylamine (400 µl) and a catalytic amount of 4-dimethylaminopyridine under ice-cooling, and the mixture is stirred at room temperature for one hour. To the reaction

solution are added water and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 1:2→1:4) to give (2R*,4S*)-4-{(3,5-dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester (156 mg). MS (m/z): 636 $[M+H]^+$

Example 243

(2R*,4S*)-4-{(3,5-Dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (200 mg) and 2-bromoethyl isocyanate (200 µl) are dissolved in toluene (2 ml), and the mixture is stirred at 90°C for 8 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in N,N-dimethylformamide (2 ml), and thereto is added sodium hydride (62.7 %, 100 mg) under ice-cooling. The mixture is stirred at 90°C for 30 minutes. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 1:4→0:1) to give (2R*,4S*)-4-{(3,5-dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-1-(4,5-dihydrooxazol-2-yl)-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (97 mg). MS (m/z): 617 $[M+H]^+$

Example 244

(1) 4-Aminobenzotrifluoride (100 g) and benzotriazole (74 g) are dissolved in toluene (1200 ml), and thereto is added dropwise propionaldehyde (49.3 ml) under ice-cooling, and the reaction solution is

stirred at room temperature overnight. Heptane (600 ml) is added, and the mixture is further stirred for 30 minutes. The precipitates are collected by filtration, and washed with heptane to give {[1-(benzotriazol-1-yl)propyl]-(4-trifluoromethylphenyl)}amine (140.9 g).

(2) {[1-(Benzotriazol-1-yl)propyl]-(4-trifluoromethylphenyl)}amine (140 g), (S)-vinylcarbamic acid 1-phenylethyl ester (83.5 g) and p-toluenesulfonic acid (1.66 g) are dissolved in toluene (1500 ml), and the mixture is stirred at 80°C for 3 hours. To the mixture are added a 2N aqueous sodium hydroxide solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is recrystallized from isopropyl ether to give (2R,4S)-4-((S)-1-phenylethoxycarbonylamino)-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (36.4 g). MS (m/z): 393 $[M+H]^+$

(3) (2R,4S)-4-((S)-1-Phenylethoxycarbonylamino)-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (2.25 g) is dissolved in a mixture of methanol (15 ml) and tetrahydrofuran (5 ml), and thereto is added 10 % palladium-carbon (200 mg). The mixture is stirred at room temperature under hydrogen atmosphere for 4 hours. The palladium-carbon is removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (15 ml), and thereto is added di-tert-butyl dicarbonate (1.25 g), and the mixture is stirred at room temperature overnight. The reaction solution is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→7:3) to give (2R,4S)-4-tert-butoxycarbonylamino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (2.0 g). MS (m/z): 345 $[M+H]^+$

(4) (2R,4S)-4-(tert-Butoxycarbonylamino)-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (2.0 g) and triethylamine (972 µl) are dissolved in methylene chloride (20 ml), and thereto is added triphosgene (690 mg)

under ice-cooling, and the mixture is stirred at room temperature for one hour. Ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue and benzyl alcohol (1.2 ml) are dissolved in tetrahydrofuran (30 ml), and thereto is added sodium hydride (446 mg) under ice-cooling, and the mixture is stirred at room temperature overnight. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in chloroform (10 ml), and thereto is added a 4N hydrogen chloride in ethyl acetate (10 ml), and the mixture is stirred at room temperature for one hour. To the reaction solution are ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R,4S)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.73 g). MS (m/z): 379: $[M+H]^+$

(5) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.73 g) and 5-bromo-2-chloropyrimidine (2.21 g) are dissolved in 1,4-dioxane (20 ml), and thereto is added N,N-diisopropylethylamine (1.99 ml), and the mixture is refluxed overnight. To the reaction solution are added a saturated brine and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-(5-bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.02 g). MS (m/z): 535/537

$[M+H]^+$

(6) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.0 g) is dissolved in N,N-dimethylformamide (15 ml), and thereto is added sodium hydride (177 mg) under ice-cooling. The mixture is stirred at the same temperature for 20 minutes, and thereto is added 3,5-bis(trifluoromethyl)benzyl bromide (1.03 ml), and the mixture is stirred at the same temperature for one hour. To the reaction solution are added ethyl acetate and water, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.19 g). MS (m/z): 761/763 $[M+H]^+$

(7) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.15 g), isonipecotic acid ethyl ester (634 µl), sodium tert-butoxide (407 mg) and 2-(di-tert-butylphosphino)biphenyl (337 mg) are dissolved in toluene (20 ml), and thereto is added tris(dibenzylideneacetone)dipalladium (258 mg), and the mixture is separated. The mixture is stirred at room temperature under nitrogen atmosphere overnight. To the reaction solution are added ethyl acetate and water, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonylpiperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.30 g). MS (m/z): 838 $[M+H]^+$

(8) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.28 g) is dissolved in ethanol (15 ml), and thereto is added 10 % palladium-carbon (200 mg), and the mixture is stirred at room temperature under hydrogen atmosphere for 1.5 hour. The palladium-carbon is removed by filtration, and the obtained filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonylpiperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinoline (1.02 g). MS (m/z): 704 $[M+H]^+$

(9) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (250 mg) and triethylamine (60 µl) are dissolved in methylene chloride (3 ml), and thereto is added triphosgene (42 mg) under ice-cooling. The mixture is stirred at room temperature for 30 minutes, and thereto are added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by tetrahydrofuran (1 ml), and thereto are added a 2-fluoroethanol (0.5 ml), triethylamine (0.5 ml) and 4-dimethylaminopyridine (10 mg), and the mixture is stirred at room temperature overnight. To the mixture are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonylpiperidin-1-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-fluoroethyl ester (215 g). MS (m/z): 794 $[M+H]^+$

Examples 245-247

The corresponding starting compounds are treated in a similar manner to Example 244 (9) to give the compounds as listed in Table 31.

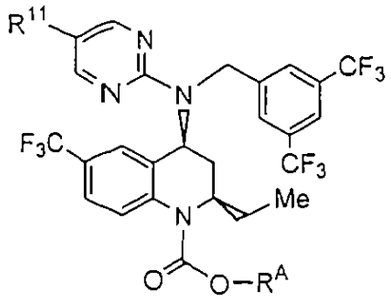
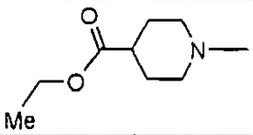
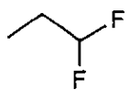
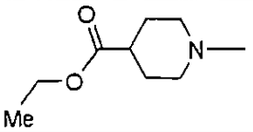
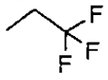
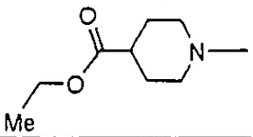
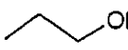


Table 31

Ex. No.	R^{11}	R^A	Physical properties, etc.
245			MS (m/z): 812 $[M+H]^+$
246			MS (m/z): 830 $[M+H]^+$
247			MS (m/z): 792 $[M+H]^+$

Example 248

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (4.87 g), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (140 mg), potassium acetate (1.88 g), and bis(pinacolate)diboron (3.25 g) are dissolved in dimethylsulfoxide (45 ml), and the mixture is stirred at 80°C under nitrogen atmosphere for one hour. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved

in tetrahydrofuran (50 ml), and thereto is added dropwise a 30 % aqueous hydrogen peroxide solution (10 ml) under ice-cooling. One hour thereafter, a saturated aqueous sodium thiosulfate solution is added to the reaction mixture under ice-cooling, and the excess amount of hydrogen peroxide is consumed. Water and ethyl acetate are added to the reaction mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.73 g). MS (m/z): 699 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.71 g) and 4-bromobutyric acid ethyl ester (617 µl) are dissolved in N,N-dimethylformamide (10 ml), and thereto is added potassium carbonate (644 mg), and the mixture is stirred at 45°C overnight. Ethyl acetate and a saturated brine are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.78 g). MS (m/z): 813 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.77 g) is dissolved in ethanol (30 ml), and thereto is added 10 % palladium-carbon (500 mg), and the mixture is stirred at room temperature under hydrogen atmosphere for 3

hours. The palladium-carbon is removed by filtration, and the obtained filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate =95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinoline (2.23 g). MS (m/z): 679 $[M+H]^+$

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetra-hydroquinoline (319 mg) and triethylamine (79 µl) is dissolved in methylene chloride (2 ml), and thereto is added triphosgene (56 mg) under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. To the mixture are added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in tetrahydrofuran (1 ml), and thereto are added 2-fluoroethanol (0.5 ml), triethylamine (0.5 ml) and 4-dimethylaminopyridine (10 mg), and the mixture is stirred at room temperature overnight. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-fluoroethyl ester (173 mg). MS (m/z): 769 $[M+H]^+$

Examples 249-253

The corresponding starting compounds are treated in a similar manner to Example 248 (4) to give the compounds as listed in Table 32.

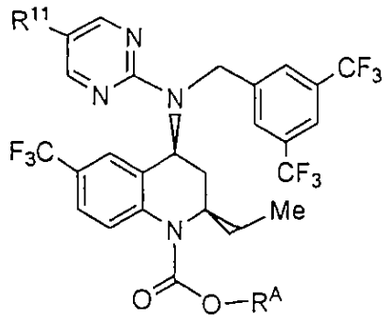
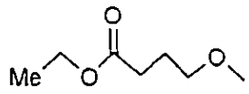
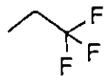
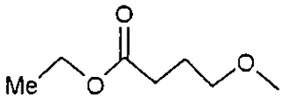
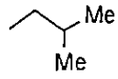
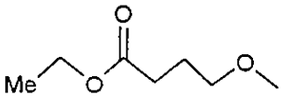
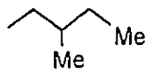
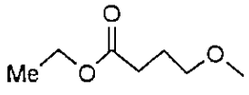
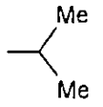
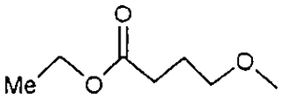
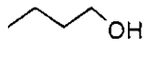


Table 32

Ex. No.	R^{11}	R^A	Physical properties, etc.
249			MS (m/z): 805 $[M+H]^+$
250			MS (m/z): 779 $[M+H]^+$
251			MS (m/z): 793 $[M+H]^+$
252			MS (m/z): 765 $[M+H]^+$
253			MS (m/z): 781 $[M+H]^+$

Examples 254-261

The corresponding starting compounds are treated in a similar manner to Example 177 (3) to give the compounds as listed in Table 33.

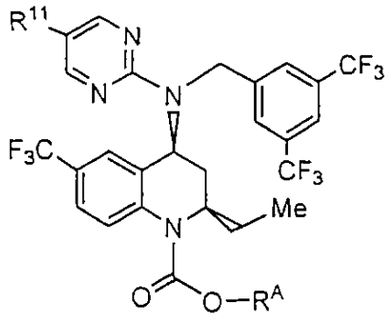
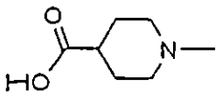
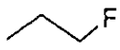
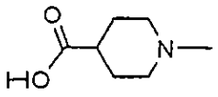
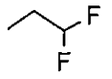
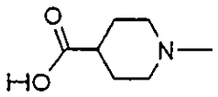
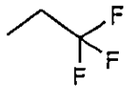
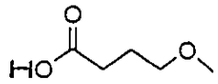
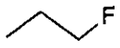
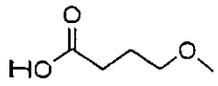
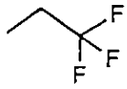
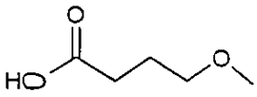
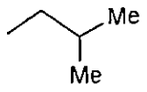
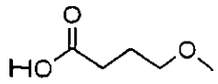
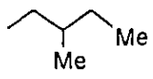
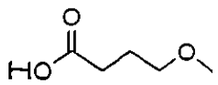
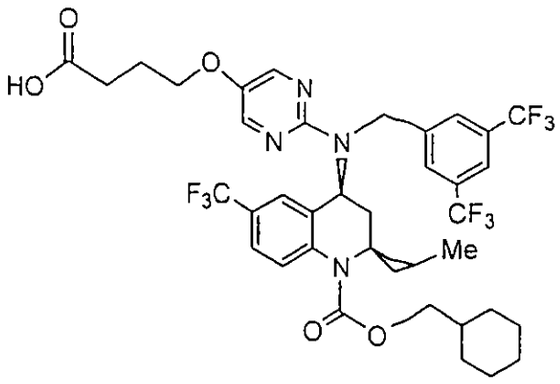


Table 33

Ex. No.	R^{11}	R^A	Physical properties, etc.
254			MS (m/z): 766 $[M+H]^+$
255			MS (m/z): 784 $[M+H]^+$
256			MS (m/z): 802 $[M+H]^+$
257			MS (m/z): 741 $[M+H]^+$
258			MS (m/z): 777 $[M+H]^+$
259			MS (m/z): 751 $[M+H]^+$
260			MS (m/z): 765 $[M+H]^+$
261			MS (m/z): 737 $[M+H]^+$

Example 262



The corresponding starting compound is treated in a similar manner to Example 248 (4) and Example 177 (3) to give the compound of Example 262. MS (m/z): 791 $[M+H]^+$

Example 263

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester (215 mg) is dissolved in tetrahydrofuran (2 ml), and thereto is added a 1N aqueous sodium hydroxide solution (2 ml), and the mixture is stirred at 50°C for 2 hours. The reaction solution is cooled to room temperature, and thereto are added ethyl acetate and 1N hydrochloric acid, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:4) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-carboxy-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester (47 mg, MS (m/z): 764 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-carboxy-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (90 mg, MS (m/z): 676 $[M+H]^+$).

Example 264

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-hydroxypropyl ester (165 mg) is dissolved in ethanol (2 ml), and thereto is added a 2N aqueous sodium hydroxide solution (317 µl), and the mixture is stirred at room temperature for 3 hours. To the mixture are added ethyl acetate and 1N hydrochloric acid, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by thin layer silica gel column chromatography (hexane:ethyl acetate = 1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-hydroxypropyl ester (37 mg, MS (m/z): 753 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-acetoxypropyl ester (116 mg, MS (m/z): 795 $[M+H]^+$).

Example 265

(1) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (7.9 g) is dissolved in N,N-dimethylformamide (35 ml), and thereto is added sodium hydride (737 mg) under ice-cooling. The mixture is stirred at the same temperature for 20 minutes, and thereto is added 3-bromomethyl-5-cyano-benzotrifluoride (5.85 g), and the mixture is stirred at the same temperature for one hour. To the reaction solution are added ethyl acetate and a saturated brine, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-[(5-bromopyrimidin-2-yl)-(3-cyano-5-trifluoromethylbenzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl

ester (4.84 g). MS (m/z): 718/720 $[M+H]^+$

(2) (2R,4S)-4-[(5-Bromopyrimidin-2-yl)-(3-cyano-5-trifluoromethyl-benzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (4.82 g), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (147 mg), and potassium acetate (1.98 g) and bis(pinacolate)diboron (2.56 g) are dissolved in dimethylsulfoxide (30 ml), and the mixture is stirred at 80°C under nitrogen atmosphere for one hour. The reaction solution is cooled to room temperature, and thereto are added ethyl acetate and a saturated brine, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (80 ml), and thereto is added dropwise a 30 % aqueous hydrogen peroxide solution (50 ml) under ice-cooling. One hour thereafter, a saturated aqueous sodium thiosulfate solution is added to the mixture under ice-cooling, and an excess amount of hydrogen peroxide is consumed. To the mixture are added ethyl acetate and water, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-[(3-cyano-5-trifluoromethylbenzyl)-(5-hydroxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.47 g). MS (m/z): 656 $[M+H]^+$

(3) (2R,4S)-4-[(3-Cyano-5-trifluoromethylbenzyl)-(5-hydroxypyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.46 g) and 4-bromobutyric acid ethyl ester (597 µl) are dissolved in N,N-dimethylformamide (20 ml), and thereto is added potassium carbonate (622 mg), and the mixture is stirred at 50°C for 5 hours. The reaction solution is cooled to room temperature, and thereto are added ethyl acetate and water, and the mixture is separated. The

organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:2) to give (2R,4S)-4-{(3-cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.29 g). MS (m/z): 770 $[M+H]^+$

(4) (2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.28 g) is dissolved in ethanol (25 ml), and thereto is added 10 % palladium-carbon (500 mg), and the mixture is stirred at room temperature under hydrogen atmosphere for one hour. The palladium-carbon is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-{(3-cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1.77 g). MS (m/z): 636 $[M+H]^+$

(5) (2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (500 mg) and triethylamine (132 µl) are dissolved in methylene chloride (5 ml), and thereto is added triphosgene (93 mg) under ice-cooling, and the mixture is stirred at room temperature for one hour. To the mixture are added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in tetrahydrofuran (5 ml), and thereto are added 2,2,2-trifluoroethanol (0.5 ml) and triethylamine (0.5 ml), and the mixture is stirred at room temperature overnight To the mixture are added water and ethyl acetate.

and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→7:3) to give (2R,4S)-4-{(3-cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester (457 mg). MS (m/z): 762 $[M+H]^+$

(6) (2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3 4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester (436 mg) is dissolved in ethanol (2 ml), and thereto is added a 2N aqueous sodium hydroxide solution (859 µl), and the mixture is stirred at room temperature for one hour. To the mixture are added ethyl acetate and a saturated aqueous citric acid solution, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate =9:1→3:2) and LC/MS (CAPCEL PAK MG II (Shiseido Co. Ltd.), water:methanol = 60:40→methanol, 40 ml/min) to give (2R,4S)-4-{[5-(3-carboxypropoxy)-pyrimidin-2-yl]-(3-cyano-5-trifluoromethylbenzyl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester (82 mg, MS (m/z): 734 $[M+H]^+$) and (2R,4S)-4-{(3-carboxy-5-trifluoromethylbenzyl)-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester (70 mg, MS (m/z): 781 $[M+H]^+$).

Example 266

(1) (2R*,4S*)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (13 g) is dissolved in N,N-dimethylformamide (100 ml), and thereto is added sodium hydride (62.7 %, 1.2 g) under ice-cooling and subsequently 3,5-

bis(trifluoromethyl)benzyl bromide (6.68 ml), and the mixture is stirred at room temperature for 17.5 hours. Water and diethyl ether are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (20.6 g). MS (m/z): 761/763 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (18.3 g), tris(dibenzylideneacetone)dipalladium (439.5 mg), 2-(di-tert-butylphosphino)diphenyl (572.3 mg), sodium tert-butoxide (3.46 g), and morpholine (3.14 ml) are dissolved in toluene (120 ml), and the mixture is stirred at room temperature for one hour. The reaction solution is stirred at 80°C for one hour. To the reaction solution is added NH-silica gel, and the mixture is filtered. To the filtrate are added a saturated aqueous sodium hydrogen carbonate solution and diethyl ether, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→6:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (11.2 g). MS (m/z): 768 $[M+H]^+$

(3) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (11.2 g) is dissolved in a mixture of tetrahydrofuran (90 ml) and methanol (30 ml), and thereto is added 10 % palladium-carbon (5 g), and the mixture is stirred under hydrogen

atmosphere for 21 hours. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is purified by NH-silica gel column chromatography (chloroform) and silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (8.9 g). MS (m/z): 634 $[M+H]^+$

(4) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (300 mg) is dissolved in methylene chloride (2.5 ml), and thereto are added triethylamine (197 µl) and triphosgene (147 mg), and the mixture is stirred at room temperature for 2 hours and 40 minutes. The reaction solution is concentrated, and the residue is dissolved in tetrahydrofuran (2.5 ml), and thereto are added triethylamine (0.6 ml), a catalytic amount of 4-(dimethylamino)pyridine, and pentane-1,5-diol (0.6 ml), and the mixture is stirred at room temperature for 14 hours. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-hydroxypentyl ester (261 mg). MS (m/z): 764 $[M+H]^+$

Example 267

(1) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (500 mg) is dissolved in methylene chloride (3 ml), and thereto are added triethylamine (212 µl) and triphosgene (150 mg), and the mixture is stirred at room temperature for 2 hours. The reaction solution is concentrated under reduced pressure, and thereto are added a saturated

aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (5 ml), and thereto are added 4-hydroxymethyl-1-tert-butoxycarbonylpiperidine (204 mg) and sodium hydride (30 mg), and the mixture is stirred at room temperature for 3 days. To the mixture are added a saturated brine and ethyl acetate, and the mixture is separated. The organic layer is dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→3:2) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid (1-tert-butoxycarbonylpiperidin-4-yl)methyl ester (282 mg). MS (m/z): 875 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid (1-tert-butoxycarbonylpiperidin-4-yl)methyl ester (282 mg) is dissolved in ethyl acetate (3 ml), and thereto is added a 4N hydrogen chloride in ethyl acetate (1 ml), and the mixture is stirred at room temperature overnight. To the mixture are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 9:1→7:3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid piperidin-4-ylmethyl ester (38 mg). MS (m/z): 775 $[M+H]^+$

Example 268

(1) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-

yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (13.7 g) is dissolved in methylene chloride (100 ml), and the mixture is cooled to -70°C, and thereto is added dropwise boron tribromide (1M methylene chloride solution, 41.4 ml) under nitrogen atmosphere. The reaction solution is gradually warmed to room temperature with stirring over a period of 1.5 hour. The mixture is further stirred at room temperature for 21 hours. To the reaction solution are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 19:1→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.1 g). MS (m/z): 647/649 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.1 g), imidazole (0.98 g), and tert-butyldimethylsilyl chloride are dissolved in N,N-dimethylformaldehyde (25 ml), and the mixture is stirred at room temperature for 15.5 hours. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-6-(tert-butyldimethylsilanyloxy)-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.88 g). MS (m/z): 761/763 $[M+H]^+$

(3) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-6-(tert-butyldimethylsilanyloxy)-2-ethyl-3,4-dihydro-2H-

quinoline-1-carboxylic acid ethyl ester (3.85 g), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (111 mg), potassium acetate (1.5 g) and bis(pinacolate)diboron (1.9 g) are dissolved in deaerated dimethylsulfoxide (50 ml), and the mixture is stirred at 80°C for 30 minutes. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (15 ml), and thereto is added a 30 % aqueous hydrogen peroxide solution (3.4 ml) under ice-cooling, and the mixture is stirred for one hour and 45 minutes. A saturated aqueous sodium thiosulfate solution and ethyl acetate are added to the mixture under ice-cooling, and the mixture is separated, The organic layer is washed with water and a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.0 g). MS (m/z): 585 $[M+H]^+$

(4) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.0 g) is dissolved in N,N-dimethylformamide (10 ml), and thereto is added sodium hydride (62.7 %, 144 mg) under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. To the reaction solution is added 4-bromobutyric acid ethyl ester (502 µl), and the mixture is stirred at room temperature for 6 hours. To the reaction solution are added water and ethyl acetate under ice-cooling, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give

(2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)-pyrimidin-2-yl]}amino-6-(3-ethoxycarbonylpropoxy)-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (578 mg). MS (m/z): 813 $[M+H]^+$

(5) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonyl-propoxy)pyrimidin-2-yl]}amino-6-(3-ethoxycarbonylpropoxy)-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) is dissolved in ethanol (1.75 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.55 ml), and the mixture is stirred at room temperature for 3 hours. To the mixture are added a 2N hydrochloric acid (0.55 ml) and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)-pyrimidin-2-yl]}amino-6-(3-carboxypropoxy)-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (207 mg) MS (m/z): 757 $[M+H]^+$

Example 269

(1) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1.0 g), and triethylamine (424 µl) are dissolved in methylene chloride (6.5 ml), and thereto is added triphosgene (300 mg) under ice-cooling, and the mixture is stirred at room temperature for 2 hours. The reaction solution is concentrated under reduced pressure, and to the residue are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue and 2-bromoethanol (1 ml) are dissolved in tetrahydrofuran (10 ml), and thereto are added triethylamine (460 µl) and a catalytic amount of 4-dimethylaminopyridine, and the mixture is stirred at room temperature for

3 days. To the reaction solution are added a saturated brine and ethyl acetate, and the mixture is separated The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-bromoethyl ester (1.51 g) as a crude product. MS (m/z): 784/786 $[M+H]^+$

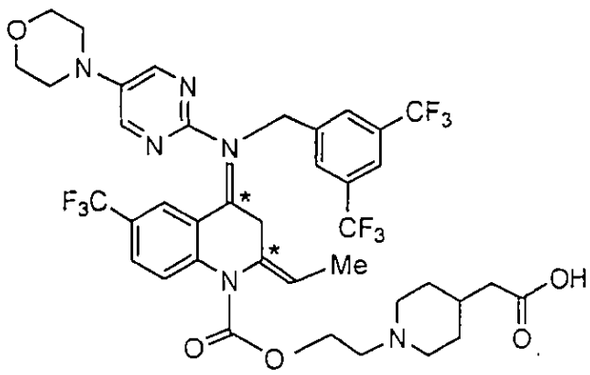
(2) The crude (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-bromoethyl ester (750 mg) is dissolved in N,N-dimethylformamide (5 ml), and thereto are added piperidine-4-carboxylic acid ethyl ester (442 µl) and potassium carbonate (400 mg), and the mixture is stirred at 60°C overnight. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-(4-ethoxycarbonylpiperidin-1-yl)ethyl ester (439 mg). MS (m/z): 861 $[M+H]^+$

(3) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-(4-ethoxycarbonylpiperidin-1-yl)ethyl ester (439 mg) is dissolved in ethanol (8 ml), and thereto is added dropwise a 1N aqueous sodium hydroxide solution (4 ml), and the mixture is stirred at room temperature overnight. To the reaction solution are added a 1N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium

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sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-(4-carboxypiperidin-1-yl)ethyl ester (307 mg). MS (m/z): 833 $[M+H]^+$

Example 270



The corresponding starting compounds are treated in a similar manner to Example 269 to give the compound of Example 270. MS (m/z): 847 $[M+H]^+$

Example 271

(1) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-hydroxypentyl ester (200 mg) is dissolved in dichloromethane (1.5 ml), and thereto is added [1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one] (124 mg), and the mixture is stirred at room temperature for 30 minutes. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→3:2) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-

1-carboxylic acid 4-formylbutyl ester (104 mg). MS (m/z): 762 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-formylbutyl ester (100 mg) is dissolved in a mixture of tert-butanol:water (4:1, 1.5 ml), and thereto are added 2-methyl-2-butene (77 µl), sodium dihydrogenphosphate dihydrate (28 mg) and sodium chlorite (47 mg) at room temperature, and the mixture is stirred for 1.5 hour. To the reaction solution are added a 1N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→19:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester (43.1 mg). MS (m/z): 778 $[M+H]^+$

Example 272

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3 g) is dissolved in tetrahydrofuran:ethanol (1:1, 30 ml), and thereto is added sodium hydroxide (858 mg), and the mixture is stirred at 80°C for 9 hours. The reaction solution is cooled to room temperature, and thereto is added a 1N hydrochloric acid (22 ml), and the mixture is concentrated under reduced pressure. To the resulting residue are added water and diethyl ether, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→3:1) and NH-silica gel column chromatography (hexane:ethyl acetate = 9:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-

yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1.79 g). MS (m/z): 626/628 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (800 mg) is dissolved in dichloromethane (6 ml), and thereto is added triethylamine (444 µl) and triphosgene (303 mg), and the mixture is stirred at room temperature for 5 hours. The reaction solution is concentrated under reduced pressure, and the insoluble materials are removed by filtration with diethyl ether. The filtrate is concentrated under reduced pressure, and the resulting residue is dissolved in tetrahydrofuran (6 ml), and to the mixture are added a 60 % sodium hydride (92 mg) and 1,5-pentanediol (400 mg) under ice-cooling. The mixture is stirrd at room temperature for 30 minutes, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a 1N hydrochloric acid and water, a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-hydroxypentyl ester (643.6 mg) MS (m/z): 757/759 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-hydroxypentyl ester (640 mg) is dissolved in acetone (5 ml), and thereto is added a 1.94M Jones reagent (1.38 ml) under ice-cooling, and the mixture is stirred for 1.5 hour. To the reaction solution are added sodium hydrogenesulfite and water under ice-cooling, and the mixture is concentrated under reduced pressure. To the resulting residue is added 1N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The

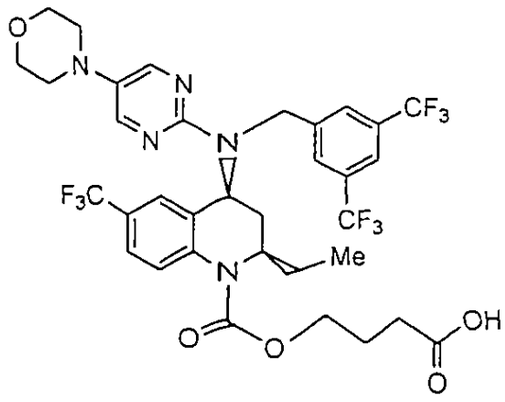
resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester (517.2 mg). MS (m/z): 771/773 $[M+H]^+$

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester (510 mg) is dissolved in tetrahydrofuran: methanol (5:1, 6 ml), and thereto is added a 2M solution of trimethylsilyldiazomethane in hexane (0.86 ml) under ice-cooling, and the mixture is stirred for one hour and 40 minutes. The reaction solution is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (466 mg). MS (m/z): 785/787 $[M+H]^+$

(5) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (460 mg) is dissolved in toluene (3.5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (54 mg) 2-(di-tert-butylphosphino)biphenyl (36 mg), sodium tert-butoxide (112 mg) and morpholine (102 µl), and the mixture is stirred at room temperature for 3 hours. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated aqueous citric acid solution and water, a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-

carboxybutyl ester (72.5 mg). MS (m/z): 778 $[M+H]^{+}$###

Example 273



The corresponding starting compound is treated in a similar manner to Example 272 to give the compound of Example 273. MS (m/z): 764 $M+H]^{+}$

Example 274

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 6-methoxycarbonylhexyl ester (574 mg), which is obtained by treating the corresponding starting compounds in a similar manner to Example 272 (1)-(4), is dissolved in toluene (4.5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (0) (65 mg), 2-(di-tert-butylphosphino)biphenyl (84 mg), morpholine (123 µl), and sodium tert-butoxide (136 mg), and the mixture is stirerd at room temperature under nitrogen atmosphere for 5 hours. The reaction mixture is neutralized with a 10 % aqueous citric acid solution, and thereto is added a saturated brine, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→2:1→chloroform:methanol = 100:1→19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-

3,4-dihydro-2H-quinoline-1-carboxylic acid 6-methoxycarbonylhexyl ester (119 mg). MS (m/z): 820[M+H]+

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 6-methoxycarbonylhexyl ester (116 mg) is dissolved in a mixture of tetrahydrofuran (2 ml) and methanol (1 ml), and to the mixture is added a 1M aqueous sodium hydroxide solution (1 ml), and the mixture is stirred at room temperature for one hour. The reaction mixture is acidified with a 10 % aqueous citric acid solution, and thereto is added a saturated brine, and the mixture is extracted with ethyl acetate The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 6-carboxyhexyl ester (85 mg). MS (m/z): 806 [M+H]+

Example 275

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.01 g) is dissolved in chloroform (20 ml), and thereto is added trimethylsilyl iodide (5 g), and the mixture is stirred under nitrogen atmosphere at 55°C overnight. To the reaction mixture is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (2.22 g). MS (m/z):626/628

254

$[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (500 mg) is dissolved in dichloromethane (4 ml), and thereto are added triethylamine (556 µl) and triphosgene (380 mg), and the mixture is stirred at room temperature for 1.5 hour. The reaction solution is concentrated under reduced pressure, and thereto is added diethyl ether, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and the resulting residue is dissolved in tetrahydrofuran (4 ml), and thereto are added 6-hydroxyhexanonic acid ethyl ester (156 µl) and triethylamine (167 µl), and the mixture is stirred at room temperature for 30 minutes. To the mixture is added a 60 % sodium hydride (38 mg) under ice-cooling, and the mixture is stirred for 30 minutes. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a 1N hydrochloric acid and water, a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline -1-carboxylic acid 5-ethoxycarbonylpentyl ester (380 mg). MS (m/z): 813/815 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (370 mg) is dissolved in toluene (2.5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (42 mg), 2-(di-tert-butylphosphino)biphenyl (27 mg), sodium tert-butoxide (87 mg) and morpholine (79 µl), and the mixture is stirred at room temperature for 30 minutes. The mixture is stirred at 80°C for one hour and 45 minutes. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is

washed with a 1N hydrochloric acid and water, a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (90.3 mg, MS (m/z): 820 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester (67.7 mg, MS (m/z): 792 $[M+H]^+$).

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (90 mg) is dissolved in ethanol (1 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.16 ml), and the mixture is stirred at room temperature for 2 hours. To the reaction solution are added a 1N hydrochloric acid (0.32 ml) and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester (53 mg). MS (m/z): 792 $[M+H]^+$

Example 276

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1 g) is dissolved in toluene (3.5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (137 mg), 2-(di-tert-butylphosphino)biphenyl (95 mg), sodium tert-butoxide (460mg) and morpholine (0.28 ml), and the mixture is

stirred at room temperature for 17 hours. To the reaction solutin are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (780.3 mg). MS (m/z): 634 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (300 mg) is dissolved in dichloromethane (2 ml), and thereto are added triethylamine (310 µl) and triphosgene (208 mg), and the mixture is stirred at room temperature for one hour. The reaction solution is concentrated under reduced pressure, and thereto is added diethyl ether, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and the resulting residue is dissolved in tetrahydrofuran (2 ml), and a 60 % sodium hydride (36 mg) and 3-hydroxypropionic acid tert-butyl ester (131 µl) are added thereto under ice-cooling. The mixture is stirred at room temperature for 16 hours, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (207 mg). MS (m/z): 806 $[M+H]^+$

(3) To (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-

quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (200 mg) is added a 4N hydrogen chloride in 1,4-dioxane (2 mL), and the mixture is stirred for 2 hours. The reactin solution is concentrated and the resulting residue is purified by silica gel column chromatography (chloroform: methanol = 1:0→19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester (176.3 mg). MS (m/z): 750 $[M+H]^+$

Example 277

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (250 mg) is dissolved in methylene chloride (3 ml), and thereto is added triethylamine (111 µl), and further added under ice-cooling triphosgene (316 mg). Under nitrogen atmosphere, the mixture is stirred at the same temperature for one hour, and the reaction mixture is concentrated under reduced pressure. To the residue is added ether, and the precipitated insoluble materials are removed by filtation. The filtrate is concentrated under reduced pressure, and to the resulting residue are added tetrahydrofuran (4 ml), methyl glycolate (62 µl) and sodium hydride (62.7 %, 30 mg), and the mixture is stirred under nitrogen atmosphere at room temperature for 2 hours. The reaction mixture is neutralized with a 10 % aqueous citric acid solution, and thereto is added a saturated brine, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid methoxycarbonylmethyl ester (166 mg). MS (m/z): 750 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-

pyrimidin-2-yl}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid methoxycarbonylmethyl ester (163 mg) is dissolved in a mixture of tetrahydrofuran (2 ml) and methanol (2 ml), and thereto is added a 1N aqueous sodium hydroxide solution (1 ml), and the mixture is stirred at room temperature for one hour. The reaction mixture is acidified with a 10 % aqueous citric acid solution, and thereto is added a saturated brine, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid carboxymethyl ester (125 mg). MS (m/z): 736 $[M+H]^+$

Examples 278-282

The corresponding starting compounds are treated in a similar manner to Example 277 to give the compounds as listed in Table 34.

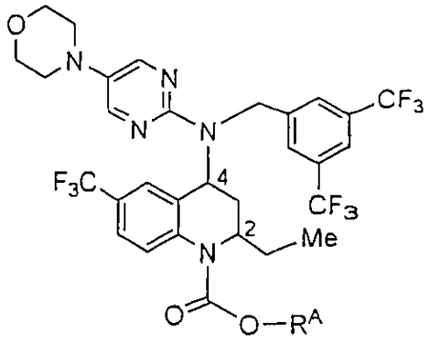
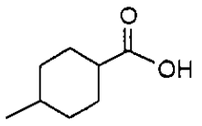
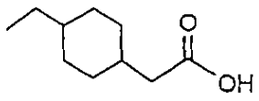
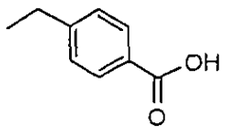
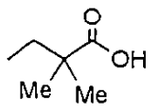
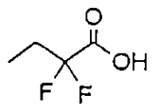


Table 34

Ex. No.	Configuration	R^A	Physical properites. etc.
278	(2R*,4S*)		MS (m/z): 804 $[M+H]^+$

279	(2R*,4S*)		MS (m/z): 832 $[M+H]^+$
280	(2R*,4S*)		MS (m/z): 812 $[M+H]^+$
281	(2R,4S)		MS (m/z): 778 $[M+H]^+$
282	(2R,4S)		MS (m/z): 786 $[M+H]^+$

Example 283

To (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid [(2S,4R)-(1-tert-butoxycarbonyl-2-methoxycarbonyl)pyrrolidin-4-yl] ester (230 mg), which is prepared by treating the corresponding starting compounds in a similar manner to Example 277 (1), is added a 4N hydrogen chloride in 1,4-dioxane (1.5 ml), and the mixture is stirred at room temperature for one hour and 40 minutes. The reaction solution is concentrated under reduced pressure, and the resulting crude product (223 mg) is dissolved in methanol (3 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.4 ml), and the mixture is stirred at room temperature for 3.5 hours. To the reaction solution is added a 1N hydrochloric acid (0.14 ml), and the mixture is concentrated under reduced pressure. To the resulting residue is added diethyl ether, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and to the resulting residue are added water and ethyl acetate, and the mixture is separated. The organic layer is concentrated under reduced pressure, and to the residue are added hexane and diethyl ether, and the mixture is dissolvd with heating. The mixture is cooled to

room temperature, and the resulting powdery product is dried under reduced pressure to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid [(2S,4R)-2-carboxypyrrolidin-4-yl] ester (116 mg). MS (m/z): 791 $[M+H]^+$

Example 284

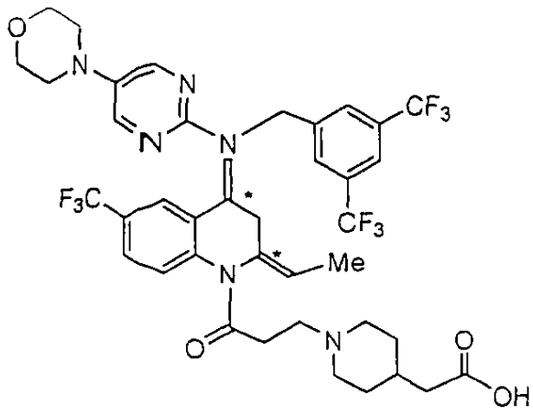
(1) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (2.0 g) is dissolved in tetrahydrofuran (30 ml), and thereto are added acryloyl chroride (770 µl) and triethylamine (1.4 ml) under ice-cooling, and the mixture is stirerd at room temperature overnight. To the reaction solution are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→3:2) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-1-acryloyl-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (1.52 g). MS (m/z): 688 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-1-acryloyl-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (500 mg) is dissolved in tetrahydrofuran (5 ml), and thereto is added piperidine-4-carboxylic acid ethyl ester (1.1 ml), and the mixture is stirred at 45°C for 3 days. To the reaction solution are added a saturated aqueous ammonium chloride solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-1-[2-(4-

ethoxycarbonylpiperidin-1-yl)ethyl]carbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (539 mg). MS (m/z): 845 $[M+H]^+$

(3) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-1-[2-(4-ethoxycarbonylpiperidin-1-yl)-ethyl]carbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (150 mg) is dissolved in ethanol (4 ml), and thereto is added dropwise a 1N aqueous sodium hydroxide solution (2 ml), and the mixture is stirred at room temperature overnight. To the reaction solution are added a 1N hydrochloric adid and ethyl acetate, and the mixture is separated The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 49:1→17:3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-1-[2-(4-carboxypiperidin-1-yl)ethyl]carbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (128 mg). MS (m/z): 817 $[M+H]^+$.

Example 285



The corresponding starting compound is treated in a similar manner to Example 284 to give the compound of Example 285. MS (m/z): 831 $[M+H]^+$

Example 286

(1) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-

pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (670 mg) is dissolvd in dichloromethane (5 ml), and thereto are added pyridine (342 µl) and 4-chlorocarbonylbutyric acid methyl ester (440 µl), and the mixture is stirred at room temperature for 24 hours. To the reaction solution are added water and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-1-(3-methoxycarbonylpropyl)carbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (460.3 mg). MS (m/z): 762 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-1-(3-methoxycarbonylpropyl)carbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (100 mg) is dissolvd in a mixture of tetrahydrofuran:methanol (1:1, 2 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.2 ml), and the mixture is stirrred for 7.5 hours. To the reaction solution is added a 2N hydrochloric acid (0.2 ml), and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-1-(3-carboxypropyl)carbonyl-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (92.6 mg). MS (m/z): 748 $[M+H]^+$

Example 287

(1) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-1-(3-methoxycarbonylpropyl)carbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (450 mg) is dissolved in tetrahydrofuran (6 ml), and thereto is added a 1M solution of borane-

tetrahydrofuran complex in tetrahydrofuran (2.95 ml) under ice-cooling, and the mixture is stirred at room temperature for 2 hours. To the reaction solution is added an aqueous diethyl ether, and the mixture is stirred for 30 minutes. To the mixture are added ethyl acetate and water, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-1-(4-methoxycarbonylbutyl)-6-trifluoromethyl-3,4-dihydro-2H-quinoline (90.0 mg). MS (m/z): 747 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-1-(4-methoxycarbonylbutyl)-6-trifluoromethyl-3,4-dihydro-2H-quinoline (85 mg) is dissolved in a mixture of tetrahydrofuran:methanol (1:1, 2 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.16 ml), and the mixture is stirred for 4.5 hours. To the reaction solution is added a 2N hydrochloric acid (0.16 ml), and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→19:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)-benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-1-(4-carboxybutyl)-6-trifluoromethyl-3,4-dihydro-2H-quinoline (82 mg). MS (m/z): 732 $[M-H]^-$

Example 288

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1 g) is dissolved in toluene (5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (147 mg), 2-(di-tert-butylphosphino)biphenyl (95 mg), sodium tert-butoxide (307 mg) and a 2N

solution of dimethylamine in tetrahydrofuran (1.6 ml), and the mixture is stirred in a sealed vessel at room temperature for one hour. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (500 mg). MS (m/z): 592 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylamino-pyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (470 mg) is treated in a similar manner to Example 276 (2)-(3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester (195.5 mg). MS (m/z): 708 $[M+H]^+$

Example 289

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (7.00 g) is dissolved in methylene chloride (80 ml), and thereto is added triethylamine (4.2 ml), and futher added triphosgene (2.99 g) under ice-cooling. Under nitrogen atmosphere, the mixture is stirred at the same temperature for 1.5 hour, and concentrated under reduced pressure, and thereto is added ether. The precipitated insoluble materials are removed by filtration, and the filtrate is concentrated under reduced pressure. To the resulting residue are added tetrahydrofuran (80 ml), tert-butyl 3-hydroxypropionate (2.64 ml) and sodium hydride (62.7 %, 680 mg), and the mixture is stirred at room temperature under nitrogen atmosphere overnight. The reaction mixture is neutralized with a 10 % aqueous citric acid solution, and

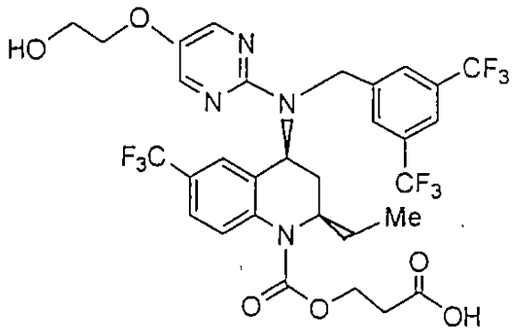
thereto is added a saturated brine. The mixture is extracted with ethyl acetate, and the organic layer is washed twice with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 10:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)-benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (6.10 g). MS (m/z): 801/799 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (5.00 g) is dissolved in dimethylsulfoxide (20 ml), and the mixture is deaerated. To the mixture are added [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (177 mg), potassium acetate (1.84 g) and bis(pinacolato)diboron (2.38 g), and the mixture is stirred at 80°C under nitrogen atmophsere for one hour. The reaction solution is cooled to room temperature, and thereto are added a saturated brine and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (30 ml), and thereto is added dropwise a 30 % aqueous hydrogen peroxide solution (10 ml) under ice-cooling, and the mixture is stirred at the same temperature for one hour. To the reaction mixture is added a saturated aqueous sodium thiosulfate solution under ice-cooling, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (2.94 g) MS (m/z): 737 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (300 mg) is dissolved in a mixture of tetrahydrofuran (2.5 ml) and N,N-dimethylformamide (1 ml), and thereto are added 4-bromobutyronitrile (244 µl) and potassium carbonate (281 mg), and the mixtrue is stirred at 60°C for 1.5 hour. To the reaction mixture is added a saturated brine, and the mixtrue is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by thin layer silica gel chromatography (hexane:ethyl acetate = 3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (107 mg). MS (m/z): 804 $[M+H]^+$

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (103 mg) is dissolved in methylene chloride (1 ml), and thereto is added a 4N hydrochloric acid in 1,4-dioxane (1 ml) under ice-cooling, and the mixture is stirred at room temperature for 2 hours. The reaction mixture is concentrated under reduced pressure, and thereto is added a small amount of a saturated aqueous sodium hydrogen carbonate solution, and the mixture is neutralized. Then, the mixture is made weakly acidic with a 10 % aqueous citric acid solution, and extracted with ethyl acetate, and the organic layer is washed twice with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester (71 mg). MS (m/z): 748 $[M+H]^+$

Example 290



The corresponding starting compound is treated in a similar manner to Example 289 to give the compound of Example 290. MS (m/z): 725 $[M+H]^+$

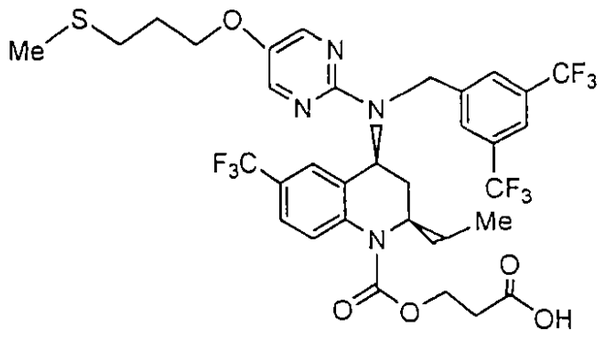
Example 291

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (220 mg) is dissolved in tetrahydrofuran (1.5 ml), and thereto is added 2-methoxyethanol (35 µl) and triphenylphosphine (118 mg), and futher added dropwise a 40 % solution of diethyl azodicarboxylate in toluene (195 µl) under cooling with water. The mixture is stirred at room temperature for one hour, and to the reaction mixture is added a saturated brine, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 17:3→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (193 mg). MS (m/z): 795 $[M+H]^+$

(2) To (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-tert-butoxycarbonylethyl ester (190 mg) is added a 4N

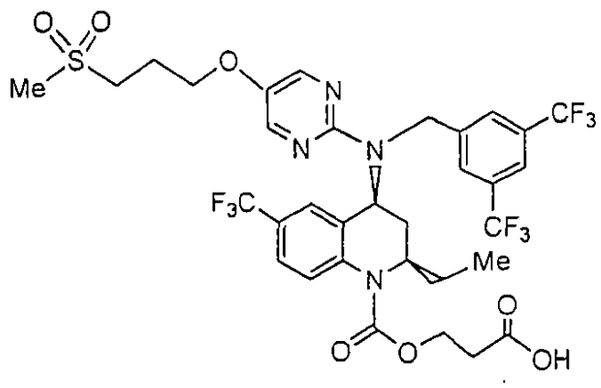
hydrochloric acid in 1,4-dioxane (2 ml), and the mixture is stirred at room temperature for 2 hours. The reaction mixture is concentrated under reduced pressure, and thereto is added a saturated brine, and the mixture is extracted with ethyl acetate. The organic layer is washed twice with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester (168 mg). MS (m/z): 739 $[M+H]^+$

Example 292



The corresponding starting compound is treated in a similar manner to Example 291 to give the compound of Example 292. MS (m/z): 769 $[M+H]^+$

Example 293



The corresponding starting compound is treated in a similar manner

to Example 50 to give the compound of Example 293. MS (m/z): 801 $[M+H]^+$

Example 294

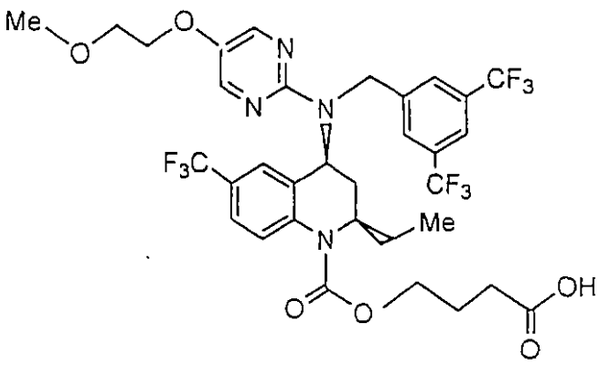
(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (1.08 g) is dissolved in dimethylsulfoxide (4 ml), and thereto are added [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium, complex with dichloromethane (1:1, 30 mg), potassium acetate (403 mg), and bis(pinacolato)diboron (522 mg), and the mixture is stirred at 80°C for 2 hours. The reaction solution is cooled to room temperature, and thereto are added water and diethyl ether, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (4 ml), and thereto is added a 30 % aqueous hydrogen peroxide solution (1.0 ml) under ice-cooling, and the mixture is stirred at room temperature for 7.5 hours. To the reaction solution is added a saturated aqueous sodium thiosulfate solution under ice-cooling, and then further added diethyl ether, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (1.06 mg). MS (m/z): 723 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (200 mg) is dissolved in tetrahydrofuran (3 ml), and thereto are added a 40 % solution of diethyl azodicarboxylate in toluene (255 ml), triphenylphosphine (147 mg), and 2-methoxyethanol (44

μl), and the mixture is stirred at room temperature for 2 hours. To the reaction solution are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→63:37) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (171.4 mg). MS (m/z): 781 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (163 mg) is dissolved in tetrahydrofuran:methanol (1:1, 4 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.315 ml), and the mixture is stirred at room temperature for 15.5 hours. To the reaction solution is added a 1N hydrochloric acid (0.63 ml), and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→24:1) and further by gel permeation column chromatography (JAIGEL-1H and JAIGEL-2H, manufactured by Japan Analytical Industry Co., Ltd.; 4 ml/min., chloroform) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester (36.5 mg). MS (m/z): 767 $[M+H]^+$

Example 295



The corresponding starting compound is treated in a similar manner to Example 294 to give the compound of Example 295. MS (m/z): 753 $[M+H]^+$

Example 296

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (400 mg) is dissolved in dimethylsulfoxide (1.5 ml), and thereto are added [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium, complex with dichloromethane (1:1, 11 mg), potassium acetate (145 mg), and bis(pinacolato)diborone (187 mg), and the mixture is stirred at 80°C for 2 hours and 20 minutes. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (1.5 ml), and thereto is added a 30 % aqueous hydrogen peroxide solution (0.56 ml) under ice-cooling, and the mixture is stirred at room temperature for 1.5 hour. To the reaction mixture is added a saturated aqueous sodium thiosulfate solution under ice-cooling, and the mixture is extracted with ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis-

(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (319 mg). MS (m/z): 751 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (310 mg) is dissolved in N,N-dimethylformamide (4 ml), and thereto are added potassium carbonate (340 mg) and 2-bromoethanol (160 µl), and the mixture is stirred at room temperature for 23.5 hours. To the reaction solution are added a saturated aqueous citric acid solution and ethyl acetate, hexane, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-hydoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (146 mg) MS (m/z): 795 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydoxyethoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (130 mg) is dissolved in ethanol (1.6 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.25 ml), and the mixture is stirred at room temperature for 4 hours. To the reaction solution is added a 2N hydrochloric acid, and the organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→19:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(2-hydoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxylpentyl ester (119 mg) MS (m/z): 767 $[M+H]^+$

Reference Example 1

To a solution of sodium azide (19.2 g) in water (75 ml) is added dropwise under ice-cooling a solution of acryloyl chloride (20 ml) in toluene (75 ml), and the mixture is stirred at the same temperature for 3 hours. A saturated aqueous sodium hydrogen carbonate solution is added thereto, and the organic layer is washed with a saturated brine and dried over magnesium sulfate. The resulting toluene solution is added dropwise into a mixture of (S)-1-phenylethyl alcohol (38.6 ml), pyridine (9.9 ml) and hydroquinone (1.49 g) which is warmed at 85°C, and the mixture is stirred at the same temperature for 2 hours. The mixture is allowed to cool to room temperature, and thereto is added a saturated aqueous sodium hydrogen carbonate solution. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 8:1) to give vinylcarbamic acid (S)-1-phenylethyl ester (28.9 g). MS (m/z): 191 $[M]^+$

Reference Example 2

(1) To a solution of p-anisidine (50 g) and benzotriazole (48.4 g) in toluene (700 ml) is added dropwise a solution of propionaldehyde (32.2 ml) in toluene (40 ml) under ice-cooling, and the mixture is stirred at room temperature overnight. To the mixture is added heptane (700 ml), and the mixture is further stirred for one hour. The precipitates are collected by filtration, washed with heptane to give {[(1-benzotriazol-1-yl)propyl]-(4-methoxyphenyl)}amine (105.8 g).

(2) {[1-(Benzotriazol-1-yl)propyl]-(4-methoxyphenyl)}amine (45.8 g), vinylcarbamic acid (S)-1-phenylethyl ester (31 g) and p-toluenesulfonic acid (616 mg) are dissolved in toluene (500 ml), and the mixture is stirred at 80°C for 4 hours. To the mixture are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and

concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 6:1→3:1) to give a mixture (46.4 g) of (2R,4S)-2-ethyl-6-methoxy-4-((S)-1-phenylethoxycarbonylamino)-1,2,3,4-tetrahydroquinoline and (2S,4R)-2-ethyl-6-methoxy-4-((S)-1-phenylethoxycarbonylamino)-1,2,3,4-tetrahydroquinoline. MS (m/z): 355 $[M+H]^+$

(3) A mixture (45.1 g) of (2R,4S)-2-ethyl-6-methoxy-4-((S)-1-phenylethoxycarbonylamino)-1,2,3,4-tetrahydroquinoline and (2S,4R)-2-ethyl-6-methoxy-4-((S)-1-phenylethoxycarbonylamino)-1,2,3,4-tetrahydroquinoline is recrystallized from isopropyl ether (150 ml) to give (2R,4S)-(2-ethyl-6-methoxy-4-((S)-1-phenylethoxycarbonylamino)-1,2,3,4-tetrahydroquinoline (9.56 g). MS (m/z): 355 $[M+H]^+$

(4) (2R,4S)-(2-ethyl-6-methoxy-4-((S)-1-phenylethoxycarbonylamino)-1,2,3,4-tetrahydroquinoline (7.5 g) and pyridine (8.56 ml) are dissolved in methylene chloride (75 ml), and thereto is added dropwise a solution of ethyl chlorocarbonate (10.1 ml) in methylene chloride (20 ml) under ice-cooling, and the mixture is stirred at room temperature for 3 hours. The reaction solution is washed with a 1M aqueous sodium hyrdoxide solution, a 1N hyrochloric acid, and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 90:10→60:40) to give (2R,4S)-2-ethyl-6-methoxy-4-((S)-1-phenylethoxy-carbonylamino)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (7.61 g). MS (m/z): 444 $[M+NH_4]^+$

(5) To a solution of (2R,4S)-2-ethyl-6-methoxy-4-((S)-1-phenylethoxy-carbonylamino)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (9.32 g) in ethanol (100 ml) is added 10 % palladium-carbon, and the mixture is stirred under hydrogen atmosphere for 3 hours. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure to give (2R,4S)-4-amino-2-ethyl-6-methoxy-3,4-dihydro-2H-

quinoline-1-carboxylic acid ethyl ester (6.09 g). MS (m/z): 279 $[M+H]^+$

Reference Example 3

(1) 3,4-Ethylenedioxyaniline (17.68 g) and benzotriazole (13.93 g) are dissolved in toluene (200 ml), and thereto is added dropwise propionaldehyde (9.2 ml) under ice-cooling. The reaction solution is stirred at room temperature overnight To the mixture is added heptane (200 ml), and the mixture is further stirred for one hour. The precipitates are collected by filtration, and washed with heptane to give {[1-(benzotriazol-1-yl)propyl]-(3,4-ethylenedioxyphenyl)}amine (35.48 g).

(2) {[1-(Benzotriazol-1-yl)propyl]-(3,4-ethylenedioxyphenyl)}amine (30.00 g), vinylcarbamic acid benzyl ester (17.13 g), and p-toluenesulfonic acid (184 mg) are dissolved in toluene (310 ml), and the mixture is stirred at 70°C for 3 hours. To the mixture are added a 1N aqueous sodium hydroxide solution and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:acetone = 20:1) to give (2R*,4S*)-4-benzyloxycarbonylamino-2-ethyl-6,7-ethylenedioxy-1,2,3,4-tetrahydroquinoline (5.63 g). MS (m/z): 369 $[M+H]^+$

(3) ((2R*,4S*)-4-benzyloxycarbonylamino-2-ethyl-6,7-ethylenedioxy-1,2,3,4-tetrahydroquinoline (5.62 g) and pyridine (6.2 ml) are dissolved in methylene chloride (45 ml), and thereto is added dropwise a solution of ethyl chlorocarbonate (7.3 ml) in methylene chloride (15 ml) under ice-cooling, and the mixture is stirred at room temperature for 3 hours. To the reaction solution is added a 1N aqueous sodium hydroxide solution (83 ml), and the mixture is stirred at room temperature for 30 minutes. The mixture is separated and the organic layer is washed with a 1N hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution, and a saturated brine, dried over sodium sulfate, and

concentrated under reduced pressure. The residue is dissolved in ethanol (40 ml), and thereto is added dropwise water (17 ml). The precipitated crystals are collected by filtration, and washed with a mixture of ethanol-water = 7:3 to give (2R*,4S*)-2-ethyl-6,7-ethylenedioxy-4-benzyloxy-carbonylamino-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5.98 g). MS (m/z): 458 $[M+H_2O]^+$

(4) (2R*,4S*)-4-Benzyloxycarbonylamino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5.97 g) is dissolved in methanol (60 ml), and thereto are added 10 % palladium-carbon (0.5 g) and ammonium formate (2.14 g), and the mixture is stirred at 37°C for one hour. The palladium-carbon is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is dissolved in chloroform (65 ml), and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. To the resulting residue is added heptane (20 ml), and the mixture is stirred overnight. The precipitated crystals are collected by filtration and washed with heptane to give (2R*,4S*)-4-amino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.54 g). MS (m/z): 307 $[M+H]^+$

Reference Example 4

To (2R*,4S*)-6-bromo-2-ethyl-4-(benzyloxycarbonylamino)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (28.36 g), which prepared by treating the corresponding starting compounds in a similar manner to Reference Example 3 (1)-(3), is added a 25 % solution of hydrogen bromide in ethyl acetate (140 ml), and the mixture is stirred at room temperature for 45 minutes. The reaction solution is concentrated under reduced pressure, and to the residue is added ether (200 ml), and the precipitates are collected by filtration and washed with ether. The precipitates are added to a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer

is washed with a saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (ethyl acetate) and concentrated. To the residue is added heptane (150 ml), and the mixture is stirred at room temperature overnight The precipitates are collected by filtration and washed with heptane to give (2R*,4S*)-4-amino-6-bromo-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (18.46 g). MS (m/z): 327/329 $[M+H]^+$

Reference Example 5

(1) Ethyl bromopyruvate (29.9 g) and urea (13.8 g) are dissolved in ethanol (110 ml) and the mixture is refluxed for 24 hours. The reaction solution is cooled to room temperature, and concentrated under reduced pressure. To the residue are added water and ether, and the pH value of the mixture is adjusted to 10 by addition of a 2N aqueous sodium hydroxide solution. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is crystallized from isopropyl ether to give 2-aminooxazole-4-carboxylic acid ethyl ester (7.53 g). MS (m/z): 157$[M+H]^+$

(2) 2-Aminooxazol-4-carboxylic acid ethyl ester (7.3 g), tert-butyl nitrite (9.4 ml), and copper (II) chloride (9.4 g) are dissolved in acetonitrile (210 ml), and the mixture is stirred at 60-80°C for 2 hours. The reaction solution is cooled to room temperature, and thereto are added a 2N aqueous hydrochloric acid solution and methylene chloride. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→2:1) to give 2-chlorooxazole-4-carboxylic acid ethyl ester (5.57 g). MS (m/z): 176/178 $[M+H]^+$

Reference Example 6

2-Amino-4-methylthiazole-5-carboxylic acid ethyl ester (8.72 g), tert-

butyl nitrite (9.4 ml) and copper (II) chloride (9.4 g) are dissolved in acetonitrile (210 ml), and the mixture is stirred at 80°C for 2 hours. The reaction solution is cooled to room temperature, and thereto are added a 2N aqueous hydrochloric acid solution and methylene chloride, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 99:1→23:2) to give 2-chloro-4-methylthiazole-5-carboxylic acid ethyl ester (8.83 g). MS (m/z): 206/208 $[M+H]^+$

Reference Example 7

(1) 4-Oxocyclohexanecarboxylic acid ethyl ester (5 g) is dissolved in ethanol (20 ml), and thereto is added sodium hydroxide (1.29 g), and the mixture is stirred at room temperature for one hour. To the mixture is added ethyl diethylphosphonoacetate (6.4 ml), and thereto is further added dropwise a 21 % solution of sodium ethoxide in ethanol (12 ml) under ice-cooling over a period of 30 minutes. The reaction solution is stirred under ice-cooling for 3.5 hours, and concentrated under reduced pressure. To the resulting residue are added a 2N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give 4-(ethoxycarbonylmethylene)cyclohexanecarboxylic acid (2.05 g) as a crude product. MS (m/z): 213 $[M+H]^+$

(2) The crude 4-(ethoxycarbonylmethylene)cyclohexanecarboxylic acid (2.05 g) is dissolved in ethanol (20 ml), and thereto are added 10 % palladium-carbon (500 mg), ammonium formate (3.7 g) and acetic acid (4.2 ml), and the mixture is stirred at 60°C overnight. The reaction solution is cooled to room temperature, and the reaction solution is filtered. To the filtrate are added a 2N hydrochloric acid and ethyl acetate, and the mixture

is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give 4-(ethoxycarbonylmethyl)cyclohexanecarboxylic acid (1.97 g). MS (m/z): 215 $[M+H]^+$

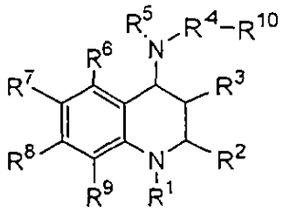
(3) 4-(Ethoxycarbonylmethyl)cyclohexanecarboxylic acid (1.97 g) is dissolved in tetrahydrofuran (20 ml), and thereto are added ethyl chlorocarbonate (650 µl) and triethylamine (950 µl) under ice-cooling, and the mixture is stirred under ice-cooling for 30 minutes. The reaction solution is filtered, and the filtrate is added to a suspension of sodium borohydride (515 mg) in tetrahydrofuran (10 ml), and the mixture is stirred under ice-cooling for one hour. A 1N hydrochloric acid and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give ethyl 4-(hydroxymethyl)cyclohexane acetate (360 mg). MS (m/z): 201 $[M+H]^+$

Reference Example 8

The corresponding starting compound is treated in a similar manner to Reference Example 3 to give (2R*,4S*)-4-amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

CLAIMS

1. A compound of the formula (I):



(I)

wherein R^1 is a hydrogen atom, an optionally substituted alkoxycarbonyl group, an optionally substituted carbamoyl group, an optionally substituted alkyl group, an optionally substituted alkanoyl group, a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), or a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted),;

R^2 is a hydrogen atom or an optionally substituted alkyl group;

R^3 is a hydrogen atom or an optionally substituted alkyl group;

R^4 is an optionally substituted alkylene group;

R^5 is a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms, wherein the heterocyclic group is substituted by 1 to 5 substituents selected from the following groups, or said heterocyclic group is substituted by 1 to 5 substituents selected from the following groups and further by a halogen atom, an oxo and/or hydroxy group:

cyano group, nitro group, carboxyl group, sulfo group, C_{3-10} alkyl group, substituted alkyl group, optionally substituted cycloalkyl group,

optionally substituted alkenyl group, C_{3-10} alkoxy group, substituted alkoxy group, optionally substituted cycloalkoxy group, optionally substituted alkoxycarbonyl group, optionally substituted carbamoyl group, optionally substituted carbamimidoyl group, optionally substituted alkylthio group, optionally substituted alkylsulfinyl group, optionally substituted alkylsulfonyl group, optionally substituted amino group, optionally substituted sulfamoyl group, optionally substituted alkanoyl group, a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic oxy group is optionally substituted), and a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonyl group is optionally substituted);

R^6, R^7, R^8 and R^9 are independently a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a cyano group, an optionally substituted alkyl group, an optionally substituted alkoxy group, an optionally substituted alkylsulfonyloxy group or an optionally substituted amino group; or

R^6 and R^7, or R^7 and R^8, or R^8 and R^9 may combine at the ends to form an alkylene group which alkylene group may contain 1 to 3 heteroatoms selected independently from nitrogen, sulfur and oxygen atoms, and may have a substituent(s); and

R^{10} is an aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the aromatic ring is optionally substituted), or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R^5 is a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms, wherein the heterocyclic group is substituted by 1 to 5 substituents selected from the following groups, or said heterocyclic group is substituted by 1 to 5 substituents selected from the following groups along with halogen atom, oxo and/or hydroxy group:

cyano group, nitro group, carboxyl group, sulfo group, C_{3-10} alkyl group, substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted alkenyl group, C_{3-10} alkoxy group, substituted alkoxy group, optionally substituted cycloalkoxy group, optionally substituted alkoxycarbonyl group, carbamoyl group, optionally substituted mono- or di-alkylcarbamoyl group, optionally substituted carbamimidoyl group, optionally substituted alkylthio group, optionally substituted alkylsulfinyl group, optionally substituted alkylsulfonyl group, amino group, optionally substituted mono- or di-alkylamino group, optionally substituted alkanoylamino group, optionally substituted alkoxycarbonylamino group, optionally substituted alkylsulfonylamino group, optionally substituted mono- or di-alkylcarbamoylamino group, a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonylamino group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonylamino group is optionally substituted), sulfamoyl group, optionally substituted mono- or di-alkyl sulfamoyl group, optionally substituted alkanoyl group, a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and

nitrogen atoms (the heterocyclic oxy group is optionally substituted), and a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonyl group is optionally substituted); and

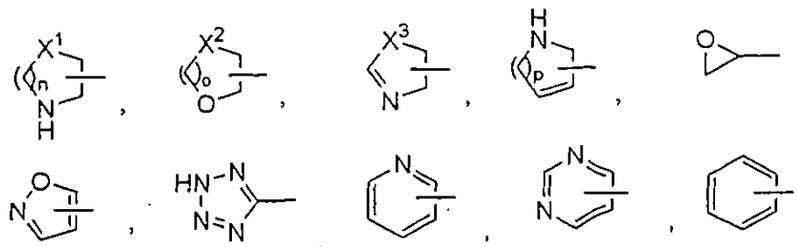
R^{10} is an aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms, which aromatic ring is optionally substituted by 1 to 4 substituents selected from the following groups: halogen atom, carboxyl group, optionally substituted alkoxycarbonyl group, carbamoyl group, optionally substituted mono- or di-alkylcarbamoyl group, optionally substituted alkyl group, optionally substituted alkoxy group, hydroxy group, nitro group, cyano group, amino group, optionally substituted mono- or di-alkylamino group, optionally substituted alkanoyl group, optionally substituted alkylthio group, and a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted).

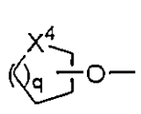
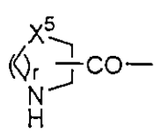
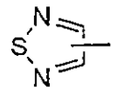
3. The compound of claim 2, wherein the substituent(s) for substituted alkyl group, optionally substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted alkenyl group, substituted alkoxy group, optionally substituted alkoxy group, optionally substituted cycloalkoxy group, optionally substituted alkoxycarbonyl group, optionally substituted mono- or di-alkylcarbamoyl group, optionally substituted alkylthio group, optionally substituted alkylsulfinyl group, optionally substituted alkylsulfonyl group, optionally substituted mono- or di-alkylamino group, optionally substituted alkanoylamino group, optionally substituted alkoxycarbonylamino group, optionally substituted alkylsulfonylamino group, optionally substituted mono- or di-alkylcarbamoylamino group, optionally substituted mono- or di-alkylsulfamoyl group, optionally substituted alkanoyl group, optionally

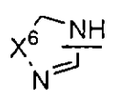
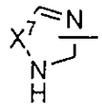
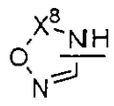
substituted alkylene group, a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonylamino group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonylamino group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic group is optionally substituted), a saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic oxy group is optionally substituted), and a saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms (the heterocyclic carbonyl group is optionally substituted) may be 1-5 groups selected from the following groups:

halogen atom; cyano group; hydroxy group; nitro group; carboxyl group; oxo group; thioxo group; sulfo group; cycloalkyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkoxycarbonyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; carbamoyl group; mono- or di-alkylcarbamoyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkanoyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkoxy group optionally substituted by

hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkanoyloxy group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkylthio group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkylsulfonyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; alkylsulfinyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; mono- or di-alkylsulfamoyl group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group: amino group; mono- or di-alkylamino group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; mono- or di-alkylsulfamoylamino group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; mono- or di-alkylureido group optionally substituted by hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, mono- or di-alkylamino group, phenyl group or morpholinyl group; and a group of the formulas:




,

,

,


,

and


wherein X^1 and X^3 are independently CH_2, NH, O, S, SO or SO_2; X^2 and X^5 are independently CH_2, O, S, SO or SO_2; X^4 is NH, O, S, SO or SO_2; X^6 and X^7 are independently O or S; X^8 is S or SO; and n, o, p, q and r are independently an integer of 1 to 4, wherein each group of the above formula is optionally substituted by 1 to 3 substituents selected from the following groups:

halogen atom, carboxyl group, hydroxy group, cyano group, oxo group, thioxo group, alkyl group, hydroxyalkyl group, alkoxycarbonylalkyl group, carboxyalkyl group, morpholinylalkyl group, phenylalkyl group, alkanoyl group, hydroxyalkanoyl group, alkoxyalkanoyl group, alkoxy group, phenylalkoxy group, alkoxycarbonyl group, benzyloxycarbonyl group, mono- or di-alkylamino group, mono- or di-alkylcarbamoyl group, mono- or di-alkylsulfamoyl group, alkylsulfonyl group and tetrazolyl group.

4. The compound of claim 3, wherein the "aromatic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, furyl, pyrimidinyl, triazolyl or thienyl group;

the "saturated or unsaturated monocyclic or bicyclic heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, hexahydroazepinyl, pyrrolinyl, imidazolidinyl, oxazolidinyl, tetrahydropyranyl, tetrahydrofuranyl, dioxolanyl, oxiranyl, pyrimidinyl, pyridyl, triazolyl, tetrazolyl, oxadiazolyl, dihydropyrimidinyl,

pyrazinyl, thiazolyl, oxazolinyl, oxazolyl, pyridazinyl, imidazolinyl, imidazolyl, pyrazinyl, thienyl, pyrrolyl, furyl or dihydrooxazinyl group;

the "saturated or unsaturated monocyclic or bicyclic heterocyclic oxy group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a morpholinyloxy, thiomorpholinyloxy piperazinyloxy, pyrrolidinyloxy, piperidinyloxy, hexahydroazepinyloxy, pyrrolinyloxy, imidazolidinyloxy, oxazolidinyloxy, tetrahydropyranyloxy, tetrahydrofuranyloxy, dioxolanyloxy, oxiranyloxy, pyrimidinyloxy, pyridyloxy, triazolyloxy, tetrazolyloxy, oxadiazolyloxy, dihydropyrimidinyloxy, pyrazinyloxy, thiazolyloxy, oxazolinyloxy, oxazolyloxy, pyridazinyloxy, imidazolinyloxy, imidazolyloxy, pyrazinyloxy, thienyloxy, pyrrolyloxy, furyloxy or dihydrooxazinyloxy group;

the "saturated or unsaturated monocyclic or bicyclic heterocyclic carbonyl group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a morpholinylcarbonyl, thiomorpholinylcarbonyl piperazinylcarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, hexahydroazepinylcarbonyl, pyrrolinylcarbonyl, imidazolidinylcarbonyl, oxazolidinylcarbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylcarbonyl, dioxolanylcarbonyl, oxiranylcarbonyl pyrimidinylcarbonyl, pyridylcarbonyl, triazolylcarbonyl, tetrazolylcarbonyl, oxadiazolylcarbonyl, dihydropyrimidinylcarbonyl, pyrazinylcarbonyl, thiazolylcarbonyl, oxazolinylcarbonyl, oxazolylcarbonyl, pyridazinylcarbonyl, imidazolinylcarbonyl, imidazolylcarbonyl, pyrazinylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, furylcarbonyl or dihydrooxazinylcarbonyl group; and

the "saturated or unsaturated monocyclic or bicyclic heterocyclic carbonylamino group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a morpholinylcarbonylamino, thiomorpholinylcarbonylamino piperazinylcarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, hexahydroazepinylcarbonyl-

amino, pyrrolinylcarbonylamino, imidazolidinylcarbonylamino, oxazolidinylcarbonylamino, tetrahydropyranylcarbonylamino, tetrahydrofuranylcarbonylamino, dioxolanylcarbonylamino, oxiranylcarbonylamino, pyrimidinylcarbonylamino, pyridylcarbonylamino, triazolylcarbonylamino, tetrazolylcarbonylamino, oxadiazolylcarbonylamino, dihydropyrimidinylcarbonylamino, pyrazinylcarbonylamino, thiazolylcarbonylamino, oxazolinylcarbonylamino, oxazolylcarbonylamino, pyridazinylcarbonylamino, imidazolinylcarbonylamino, imidazolylcarbonylamino, pyrazinylcarbonylamino, thienylcarbonylamino, pyrrolylcarbonylamino, furylcarbonylamino or dihydrooxazinylcarbonylamino group.

5. The compound of claim 1, wherein R^1 is a hydrogen atom; an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), alkylthio group, alkylsulfonyl group, alkenyl group, amino group, mono- or di-alkylamino group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group and alkoxycarbonyl group), alkanoylamino group (said alkanoylamino group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, hydroxy group and halogen atom), halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), phenyl group (said

phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), morpholinyl group optionally substituted by oxo group, piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), and pyrimidinyl group (said pyrimidinyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group); a carbamoyl group optionally substituted by alkoxy group; a dihydrooxazolyl group optionally substituted by 1 to 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; a dihydroimidazolyl group optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; a dihydrooxazinyl group optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; mono- or di-alkylcarbamoyl group optionally substituted by 1 to 5 substituents selected

independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group); an alkyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group); an alkanoyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group); a morpholinylcarbonyl group ; a piperazinylcarbonyl group optionally substituted by alkyl group, carboxyalkyl group or alkoxycarbonylalkyl group;

a pyrrolidinylcarbonyl group optionally substituted by 1 to 3 substituents

selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group; or a piperidinylcarbonyl group optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group;

R^5 is a saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms;

wherein said heterocyclic group is substituted by 1 to 4 substituents selected from the following groups, or said heterocyclic group is substituted by 1 to 4 substituents selected from the following groups along with a halogen atom, an oxo and/or hydroxy group:

cyano group;

nitro group;

carboxyl group;

sulfo group;

cycloalkyl group optionally substituted by carboxyl or alkoxycarbonyl group;

C_{3-10} alkyl group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, tetrazolyl group, mono- or di-alkylcarbamoyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, carboxyl or hydroxy group), alkanoyl group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group optionally substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, dioxolanyl group optionally substituted by alkyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group

optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group, morpholinyl group, and piperidinyloxy group optionally substituted by alkyl group;

alkenyl group optionally substituted by a group selected from cyano group, hydroxy group, carboxyl group, benzyloxycarbonyl group, and tetrazolyl group;

alkenyloxy group optionally substituted by carboxyl group;

C_{3-10} alkoxy group;

alkoxy group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by carboxyl, alkoxycarbonyl or hydroxy group), alkoxy group (said alkoxy group is optionally substituted by carboxyl, formyl or hydroxy group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, aminosulfonyl group, amino group, mono- or di-alkylamino group substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, cycloalkyl group optionally substituted by carboxymethyl group, oxiranyl group, phenyl group optionally substituted by alkoxy or carboxyl group, morpholinyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, pyrrolidinyl group substituted by oxo group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperazinyl group optionally substituted by

alkyl group, hexahydroazepinyl group, pyrimidinyl group, pyridyl group, dioxolanyl group optionally substituted by alkyl group, oxadiazolyl group optionally substituted by oxo group, oxathiadiazolyl group optionally substituted by oxo group, pyrrolidinylcarbonyl group optionally substituted by carboxyl group, piperidinyloxy group optionally substituted by alkyl group, and morpholinylcarbonyl group;

alkoxycarbonyl group optionally substituted by phenyl group;

carbamoyl group;

mono- or di-alkylcarbamoyl group optionally substituted by a group selected from carboxyl group, morpholinyl group and alkoxy group;

hydroxycarbamimidoyl group;

alkylthio group optionally substituted by a group selected from hydroxy group, carboxyl group and mono- or di-alkylcarbamoyl group;

alkylsulfinyl group;

alkylsulfonyl group optionally substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group and mono- or di-alkylcarbamoyl group;

amino group;

mono- or di-alkylamino group optionally substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group and morpholinyl group;

mono- or di-alkanoylamino group optionally substituted by a group selected from hydroxy group, alkoxy group, carboxyl group and amino group;

mono- or di-alkylcarbamoylamino group optionally substituted by alkoxy group;

morpholinylcarbonylamino group;

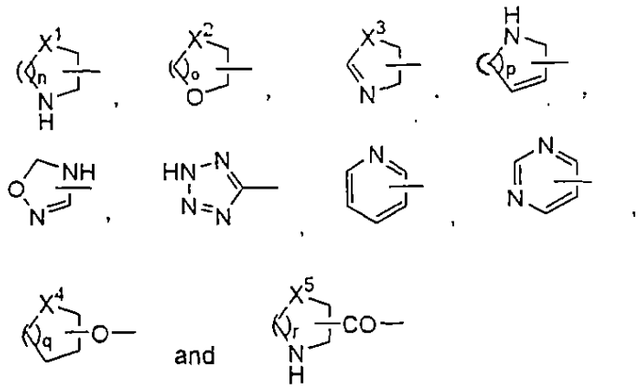
sulfamoyl group;

mono- or di-alkylsulfamoyl group;

alkanoyl group optionally substituted by a group selected from hydroxy

group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group and morpholinyl group; or

a group selected from the following groups:



and

wherein X^1 and X^3 are independently CH_2, NH, O, S, SO or SO_2; X^2 and X^5 are independently CH_2, O, S, SO or SO_2; X^4 is NH, O, S, SO or SO_2; and n, o, p, q and r are independently an integer of 1 to 4, wherein each group of the above formula is optionally substituted by a substituent(s) selected from the following groups:

carboxyl group, hydroxy group, cyano group, oxo group, alkyl group, hydroxyalkyl group, alkoxycarbonylalkyl group, carboxyalkyl group, morpholinylalkyl group, phenylalkyl group, alkanoyl group, hydroxyalkanoyl group, alkoxyalkanoyl group, alkoxy group, phenylalkoxy group, alkoxycarbonyl group, benzyloxycarbonyl group, mono- or di-alkylamino group, mono- or di-alkylcarbamoyl group, mono- or di-alkylsulfamoyl group, alkylsulfonyl group and tetrazolyl group;

R^6, R^7, R^8 and R^9 are independently a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a cyano group, an alkyl group, an alkoxy group, or a mono- or di-alkylamino group, wherein said alkyl, alkoxy and mono- or di-alkylamino groups are optionally substituted by 1 to 6 substituents selected independently from halogen atom, hydroxy group, alkoxy group, alkylthio group, amino group, nitro group, cyano group, oxo

group, carboxyl group, alkoxycarbonyl group and mono- or di-alkylamino group; or

R^6 and R^7, or R^7 and R^8, or R^8 and R^9 may combine at the ends to form an alkylene group which alkylene group may contain 1 to 3 heteroatoms selected independently from nitrogen, sulfur and oxygen atoms; and

R^{10} is an aromatic monocyclic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms;

wherein the monocyclic aromatic ring is optionally substituted by 1 to 4 substituents selected independently from halogen atom, carboxyl group, alkoxycarbonyl group, carbamoyl group, mono- or di-alkylcarbamoyl group, alkyl group, alkoxy group, hydroxy group, nitro group, cyano group, amino group, mono- or di-alkylamino group, alkanoyl group, alkylthio group, tetrazolyl group and dihydrooxazolyl group, wherein the alkyl, alkoxy, mono- or di-alkylamino, mono- or di-alkylcarbamoyl, alkanoyl and alkylthio groups are optionally substituted by a substituent(s) selected independently from halogen atom, and hydroxy, alkoxy, amino, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, alkylpiperazinyl and alkanoylpiperazinyl groups.

6. The compound of claim 5, wherein the "aromatic monocyclic ring optionally containing 1 to 3 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a phenyl group, a pyridyl group, a pyrimidinyl group, a furyl group or a thienly group; and the "saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms" is a pyrimidinyl group, a pyridyl group, a triazolyl group, a tetrazolyl group, a oxadiazolyl group, a dihydropyrimidinyl group, a pyrazinyl group, a thiazolyl group, an oxazolyl group, an imidazolyl group, a dihydrooxazinyl group, a dihydropyrazinyl group or a pyrazolyl group.

7. The compound of claim 6, wherein R^1 is a hydrogen atom; an

alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), alkylthio group, alkylsulfonyl group, alkenyl group, amino group, mono- or di-alkylamino group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group and alkoxycarbonyl group), alkanoylamino group (said alkanoylamino group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, hydroxy group and halogen atom), halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), morpholinyl group optionally substituted by oxo group, piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group), pyrrolidinyl group (said pyrrolidinyl group is optionally substituted

by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), and pyrimidinyl group (said pyrimidinyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group); dihydrooxazolyl group optionally substituted by 1 to 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; or a mono- or di-alkylcarbamoyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group);

R^2 is an alkyl group;

R^3 is a hydrogen atom;

R^4 is an alkylene group;

R^5 is a heterocyclic group selected from pyrimidinyl group, pyridyl group, triazolyl group, tetrazolyl group, oxadiazolyl group, dihydropyrimidinyl group, pyrazinyl group, thiazolyl group, oxazolyl group, imidazolyl group, dihydrooxazinyl group, pyrazolyl group and dihydropyrazinyl group, wherein said heterocyclic group is substituted by 1 to 4 substituents selected from the following groups, or 1 to 4 substituents selected from the following groups and oxo group:

cyano group;

nitro group;

carboxyl group;

sulfo group,

C_{3-10} alkyl group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group , tetrazolyl group, mono- or di-alkylcarbamoyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, carboxyl or hydroxy group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group optionally substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, dioxolanyl group optionally substituted by alkyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group, morpholinyl group, and piperidinyloxy group optionally substituted by alkyl group;

alkenyl group optionally substituted by a group selected from cyano group, hydroxy group, carboxyl group, benzyloxycarbonyl group, and tetrazolyl group;

alkenyloxy group optionally substituted by carboxyl group;

C_{3-10} alkoxy group;

alkoxy group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group

optionally substituted by hydroxy group, alkoxy group optionally substituted by carboxyl or hydroxy group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, aminosulfonyl group, amino group, mono- or di-alkylamino group substituted by carboxyl or alkoxy group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, cycloalkyl group optionally substituted by carboxymethyl group, oxiranyl group, phenyl group optionally substituted by alkoxy or carboxyl group, morpholinyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, pyrrolidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, pyrrolidinyl group substituted by oxo group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonylalkyl or carboxyalkyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group, pyrimidinyl group, pyridyl group, dioxolanyl group optionally substituted by alkyl group, oxadiazolyl group optionally substituted by oxo group, oxathiadiazolyl group optionally substituted by oxo group, pyrrolidinylcarbonyl group optionally substituted by carboxyl group, piperidinyloxy group optionally substituted by alkyl group, and morpholinylcarbonyl group;

alkoxycarbonyl group optionally substituted by phenyl group;

carbamoyl group;

mono- or di-alkylcarbamoyl group optionally substituted by a group selected from carboxyl group, morpholinyl group and alkoxy group;

hydroxycarbamimidoyl group;

alkylthio group optionally substituted by a group selected from hydroxy group, carboxyl group and mono- or di-alkylcarbamoyl group;

alkylsulfinyl group;

alkylsulfonyl group optionally substituted by a group selected from

hydroxy group, carboxyl group and mono- or di-alkylcarbamoyl group;
amino group;
mono- or di-alkylamino group optionally substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group and morpholinyl group;
alkanoylamino group optionally substituted by a group selected from hydroxy group, alkoxy group, carboxyl group and amino group;
mono- or di-alkylureido group optionally substituted by alkoxy group;
morpholinylcarbonylamino group;
sulfamoyl group;
mono- or di-alkylsulfamoyl group;
morpholinyl group optionally substituted by a group selected from oxo group and carboxyl group;
optionally oxidized thiomorpholinyl group;
piperazinyl group optionally substituted by a group selected from cyano group, alkyl group, hydroxyalkyl group, alkoxycarbonylalkyl group, carboxyalkyl group, alkanoyl group, hydroxyalkanoyl group, alkoxyalkanoyl group, benzyloxycarbonyl group, mono- or di-alkylcarbamoyl group, mono- or di-alkylsulfamoyl group, alkylsulfonyl group and tetrazolyl group;
piperidinyl group optionally substituted by a group selected from carboxyl group, hydroxy group, oxo group, alkyl group, hydroxyalkyl group, carboxyalkyl group, alkanoyl group, alkoxy group, phenylalkoxy group, alkoxycarbonyl group and alkoxycarbonylalkyl group;
pyrrolidinyl group optionally substituted by a group selected from oxo group, carboxyl group, alkanoyl group and mono- or di-alkylamino group;
pyrrolinyl group optionally substituted by oxo group;
hexahydrodiazepinyl group optionally substituted by alkanoyl group;
diazolidinyl group optionally substituted by oxo group;

dioxolanyl group optionally substituted by alkyl group;

pyridyl group optionally substituted by carboxyl group, hydroxy group or hydroxyalkyl group (said pyridyl group is optionally further oxidized);

tetrazolyl group substituted by hydroxy group or alkyl group that is optionally substituted by morpholinyl group;

dihydrooxadiazolyl group optionally substituted by oxo group;

dihydroimidazolyl group;

dihydrooxazolyl group;

oxazolidinyl group optionally substituted by oxo group;

tetrahydropyridyl group optionally substituted by benzyl group;

pyrimidinyl group;

tetrahydropyranyl group;

piperidinyloxy group optionally substituted by a group selected from alkyl group, carboxyl group, carboxyalkyl group and alkanoyl group;

pyrrolidinyloxy group optionally substituted by a group selected from alkyl group, carboxyl group, carboxyalkyl group and alkanoyl group;

tetrahydropyranyloxy group;

tetrahydrofuranyloxy group;

optionally oxidized thianyloxy group;

morpholinylcarbonyl group;

piperazinylcarbonyl group optionally substituted by a group selected from alkanoyl group and alkyl group; and

pyrrolidinylcarbonyl group;

R^6 and R^9 each are a hydrogen atom;

R^7 and R^8 are independently a hydrogen atom, an alkyl group optionally substituted by halogen atom, an alkoxy group, a mono- or di-alkylamino group or halogen atom; or

R^7 and R^8 combine at the ends to form an alkylenedioxy group; and

R^{10} is a phenyl or pyridyl group, which phenyl or pyridyl group is optionally

substituted by 1 to 4 substituents selected from alkyl group optionally substituted by halogen atom, alkoxy group, hydroxy group, halogen atom, cyano group, amino group and mono- or di-alkylamino group.

8. The compound of claim 7, wherein R^1 is an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group and alkoxycarbonyl group), alkenyl group, halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), and pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group); or a dihydrooxazolyl group optionally substituted by 1 or 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group;

R^5 is a pyrimidinyl group, a pyridyl group, a triazolyl group, a tetrazolyl group, an oxadiazolyl group, a dihydropyrimidinyl group, a pyrazinyl group, a thiazolyl group, an oxazolyl group, a dihydrooxazinyl group, a pyrazolyl group or a dihydropyrazinyl group, said group being substituted by 1 to 4 substituents selected from the following groups:

cyano group;

nitro group;

carboxyl group;

sulfo group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group optionally substituted by carboxyl or hydroxy group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkenyl group optionally substituted by carboxyl group, cyano group or benzyloxycarbonyl group;

alkoxy group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group optionally substituted by carboxyl or hydroxy group, alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkoxycarbonyl group optionally substituted by phenyl group;

mono- or di-alkylcarbamoyl group optionally substituted by carboxyl group;

hydroxycarbamimidoyl group;

alkylthio group;

alkylsulfonyl group optionally substituted by carboxyl group;

mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group or morpholinyl group;

mono- or di-alkylsulfamoyl group;

morpholinyl group;

optionally oxidized thiomorpholinyl group;

piperazinyl group optionally substituted by a group selected from alkyl group, alkanoyl group and hydroxyalkanoyl group;

piperidinyl group optionally substituted by a group selected from carboxyl group, alkyl group and alkoxycarbonyl group;

dioxolanyl group optionally substituted by alkyl group;

tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl group or morpholinylalkyl group;

dihydrooxadiazolyl group optionally substituted by oxo group;

pyrimidinyl group; or

tetrahydropyranyl group; and

R^{10} is a phenyl or pyridyl group, which phenyl or pyridyl group is optionally substituted by 1 to 4 substituents selected from alkyl group optionally substituted by halogen atom, alkoxy group, hydroxy group, halogen atom, cyano group, amino group and mono- or di-alkylamino group.

9. The compound of claim 1, wherein R^1 is a hydrogen atom; an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy

group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), alkylthio group, alkylsulfonyl group, alkenyl group, amino group, mono- or di-alkylamino group, tetrazolyl group, carbamoyl group, mono- or di-alkylcarbamoyl group (said mono- or di-alkylcarbamoyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group and alkoxycarbonyl group) , alkanoylamino group (said alkanoylamino group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, hydroxy group and halogen atom), halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), morpholinyl group optionally substituted by oxo group, piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group), pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, amino group, mono- or di-alkylamino group, halogen atom, oxo group, carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group, carboxyalkoxy group and alkoxycarbonylalkoxy group), and

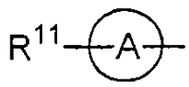
pyrimidinyl group (said pyrimidinyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyalkyl group, alkoxycarbonylalkyl group and carboxyalkoxy group, alkoxycarbonylalkoxy group); dihydrooxazolyl group optionally substituted by 1 to 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, alkyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group; or a mono- or di-alkylcarbamoyl group optionally substituted by 1 to 5 substituents selected independently from halogen atom, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, amino group, mono- or di-alkylamino group, morpholinyl group, pyridyl group, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group) and phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, amino group and hydroxy group);

R^2 is an alkyl group;

R^3 is a hydrogen atom;

R^4 is an alkylene group;

R^5 is a group of the formula:



wherein Ring A is a saturated or unsaturated 5- to 8-membered heterocyclic group containing 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen atoms,

R^{11} is a group selected from the following groups:

cyano group;

nitro group;

carboxyl group;

sulfo group;

alkyl group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, hydroxy or carboxyl group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkenyl group optionally substituted by carboxyl group, cyano group or benzyloxycarbonyl group;

alkoxy group substituted by a group selected from halogen atom, cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by phenyl, hydroxy or carboxyl group), alkanoyloxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperidinyl group optionally substituted by alkoxycarbonyl or carboxyl group, piperazinyl group optionally substituted by alkyl group, hexahydroazepinyl group and morpholinyl group;

alkoxycarbonyl group optionally substituted by phenyl group;

mono- or di-alkylcarbamoyl group optionally substituted by carboxyl group;

hydroxycarbamimidoyl group;

alkylthio group;

alkylsulfinyl group;

alkylsulfonyl group optionally substituted by carboxyl group;

mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, mono- or di-alkylamino group or morpholinyl group;

mono- or di-alkylsulfamoyl group;

morpholinyl group;

optionally oxidized thiomorpholinyl group;

piperazinyl group optionally substituted by a group selected from alkyl group, alkanoyl group and hydroxyalkanoyl group;

pyrrolidinyl group optionally substituted by carboxyl group, carboxyalkyl group, alkyl group, alkoxycarbonyl group or alkoxycarbonylalkyl group;

piperidinyl group optionally substituted by carboxyl group, carboxyalkyl group, alkyl group, alkoxycarbonyl group or alkoxycarbonylalkyl group;

dioxolanyl group optionally substituted by alkyl group;

tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl group or morpholinylalkyl group;

dihydrooxadiazolyl group optionally substituted by oxo group;

pyrimidinyl group; or

tetrahydropyranyl group;

R^6 and R^9 each are a hydrogen atom;

R^7 and R^8 are independently a hydrogen atom, an alkyl group optionally sbustituted by halogen atom, alkoxy group, or mono- or di-alkylamino group; or combine at the ends to form an alkylenedioxy group; and

R^{10} is a phenyl or pyridyl group, which phenyl or pyridyl group is optionally substituted by 1 to 4 substituents selected from alkyl group optionally substiuted by halogen atom, alkoxy group, hydroxy group, halogen atom,

cyano group, amino group and mono- or di-alkylamino group.

10. The compound of claim 9, wherein Ring A is a pyrimidinyl group, a pyridyl group, a triazolyl group, a tetrazolyl group, an oxadiazolyl group, a dihydropyrimidinyl group, a pyrazinyl group, a thiazolyl group, an oxazolyl group, a dihydrooxazinyl group, an imidazolyl group, a pyrazolyl group, or a dihydropyrazinyl group.

11. The compound of claim 10, wherein Ring A is a pyrimidinyl group, a pyridyl group, a tetrazolyl group, an oxadiazolyl group, a pyrazinyl group, a thiazolyl group or an oxazolyl group; and

R^{11} is a carboxyl group; a cyano group; a nitro group; an alkyl group substituted by a group selected from hydroxy group, cyano group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, hydroxyalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by carboxyl group, piperidinyl group optionally substituted by carboxyl group, piperazinyl group optionally substituted by alkyl group and morpholinyl group; an alkenyl group optionally substituted by carboxyl group; an alkoxy group substituted by a group selected from hydroxy group, cyano group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, hydroxyalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, pyrrolidinyl group optionally substituted by carboxyl group, piperidinyl group optionally substituted by carboxyl group, piperazinyl group optionally substituted by alkyl group and morpholinyl group; an alkoxycarbonyl group; a hydroxycarbamimidoyl

group; alkylthio group; an alkylsulfonyl group optionally substituted by carboxyl group; a mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group, alkoxy group or mono- or di-alkylamino group; a morpholinyl group; an optionally oxidized thiomorpholinyl group; a piperazinyl group optionally substituted by a group selected from alkyl group, alkanoyl group and hydroxyalkanoyl group; a pyrrolidinyl group optionally substituted by carboxyl group, alkyl group carboxyalkyl group or alkoxycarbonyl group; a piperidinyl group optionally substituted by carboxyl group, alkyl group, carboxyalkyl group or alkoxycarbonyl group; a tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl group, or morpholinylalkyl group; an oxodihydrooxadiazolyl group; a pyrimidinyl group; or a tetrahydropyranyl group.

12. The compound of claim 11, wherein R^1 is an alkoxycarbonyl group optionally substituted by 1 to 5 substituents selected independently from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group (said alkoxy group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group and alkoxycarbonyl group), alkenyl group, halogen atom, cycloalkyl group (said cycloalkyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), phenyl group (said phenyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), piperidinyl group (said piperidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group, alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group), and pyrrolidinyl group (said pyrrolidinyl group is optionally substituted by 1 to 3 substituents selected independently from hydroxy group, halogen atom, carboxyl group,

alkoxycarbonyl group, carboxyalkyl group and alkoxycarbonylalkyl group); or a dihydrooxazolyl group optionally substituted by 1 or 2 substituents selected independently from carboxyl group, alkoxycarbonyl group, carboxyalkyl group, alkoxycarbonylalkyl group and hydroxyalkyl group;

R^{10} is a phenyl group substituted by 1 to 3 substituents selected from alkyl group optionally substituted by halogen atom, alkoxy group, halogen atom and cyano group;

Ring A is a pyrimidinyl group, a pyridyl group, a tetrazolyl group, an oxadiazolyl group or a thiazolyl group; and

R^{11} is a carboxyl group; a cyano group; a nitro group; an alkyl group substituted by a group selected from hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, piperazinyl group optionally substituted by alkyl group and morpholinyl group; an alkenyl group optionally substituted by carboxyl group; an alkoxy group substituted by a group selected from cyano group, hydroxy group, carboxyl group, alkoxycarbonyl group, alkoxy group, phenylalkoxy group, carboxyalkoxy group, alkylthio group, alkylsulfonyl group, alkylsulfinyl group, amino group, mono- or di-alkylamino group, mono- or di-alkylsulfamoylamino group, mono- or di-alkylureido group optionally substituted by morpholinyl group, oxiranyl group, di-alkyldioxolanyl group, piperazinyl group optionally substituted by alkyl group and morpholinyl group; a hydroxycarbamimidoyl group; an alkylthio group; an alkylsulfonyl group optionally substituted by alkoxycarbonyl group; a mono- or di-alkylamino group optionally substituted by hydroxy group, carboxyl group or alkoxy group; a morpholinyl group; optionally oxidized thiomorpholinyl group; a piperazinyl group optionally substituted by a group selected from

alkyl group, alkanoyl group and hydroxyalkanoyl group; a pyrrolidinyl group optionally substituted by carboxyl group, alkyl group carboxyalkyl group or alkoxycarbonyl group; a piperidinyl group optionally substituted by carboxyl group, alkyl group, carboxyalkyl group or alkoxycarbonyl group; a tetrazolyl group optionally substituted by alkyl group, hydroxyalkyl group, or morpholinylalkyl group; an oxodihydrooxadiazolyl group; a pyrimidinyl group; or a tetrahydropyranyl group.

13. The compound of claim 12, wherein R^1 is an alkoxycarbonyl group optionally substituted by 1 or 5 substituents selected independently from carboxyl group, alkoxycarbonyl group, halogen atom, hydroxy group and cycloalkyl group;

R^{10} is a phenyl group substituted by 1 to 3 substituents selected from cyano group, alkyl group optionally substituted by halogen atom and alkoxy group;

Ring A is a pyrimidinyl group, a pyridyl group, a tetrazolyl group or an oxadiazolyl group;

R^{11} is a carboxyl group; an alkyl group substituted by hydroxy group, carboxyl group, alkoxy group or alkylsulfonyl group; an alkenyl group optionally substituted by carboxyl group; an alkoxy group substituted by carboxyl group, cyano group, hydroxy group, alkoxy group, alkylthio group or alkylsulfonyl group; a mono- or di-alkylamino group optionally substituted by carboxyl group or alkoxy group; a morpholinyl group; a piperidinyl group substituted by carboxyl group; or a tetrazolyl group substituted by hydroxyalkyl group;

R^7 is an alkyl group optionally sbustituted by halogen atom, alkoxy group, or mono- or di-alkylamino group; and

R^8 is a hydrogen atom.

14. The compound of claim 13, wherein R^1 is an ethoxycarbonyl group, a hydroxyethoxycarbonyl group, a 2-fluoroethoxycarbonyl group, a 2,2-difluoroethoxycarbonyl group or a 2,2,2-trifluoroethoxycarbonyl group;

R^2 is an ethyl group; R^{10} is a phenyl group substituted by 1 to 2 substituents selected from cyano group, trifluoromethyl group and methoxy group; and R^7 is a trifluoromethyl group or a methoxy group.

15. The compound of claim 13, wherein R^1 is a carboxy(C_{2-10}alkoxy)carbonyl group or an alkoxycarbonyl(C_{2-10}alkoxy)carbonyl group; R^2 is an ethyl group; R^{10} is a phenyl group substituted by 1 to 2 substituents selected from cyano group, trifluoromethyl group and methoxy group; and R^7 is a trifluoromethyl group or a methoxy group.

16. A compound selected from the following compounds or a pharmaceutically acceptable salt thereof.

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-[[3,5-Bis(trifluoromethyl)benzyl]-(5-{[methyl-(2-methoxyethyl)]-amino}pyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-carboxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-carboxyethyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[2-(2-hydroxyethyl)-2H-tetrazol-5-yl]pyrimidin-2-yl})amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid

ethyl ester;

(2R,4S)-4-{(3,5-Dimethoxybenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3,5-Dicyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyanobenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R*,4S*)-4-([3,5-Bis(trifluoromethyl)benzyl]-{5-[2-(2-hydroxyethyl)-2H-tetrazol-5-yl]pyrimidin-2-yl})amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-hydroxyethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[2-(2-methanesulphonylethyl)-2H-tetrazol-5-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-carboxyethyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-

carboxylic acid ethyl ester;

(2R,4S)-4-[[3,5-Bis(trifluoromethyl)benzyl]-(5-{[methyl-(2-carboxyethyl)]-amino}pyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-[3-(tetrazol-5-yl)-propoxy]pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxybutoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(5-carboxypentyloxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-carboxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxymethylpyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxybutoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(4-carboxybutoxy)-

pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-dimethylamino-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxtlic acid ethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(3-carboxypropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2,2,2-trifluoroethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-carboxypyperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-

yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester; and

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester.

17. A compound selected from the following compounds or a

pharmaceutically acceptable salt thereof.

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic

acid 3-carboxypropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-

dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-hydroxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;
(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic

acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-dimethylaminopyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyridin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-

carboxylic acid 2-carboxyethyl ester:

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 3-carboxypropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-

carboxy-2-methylpropyl ester;

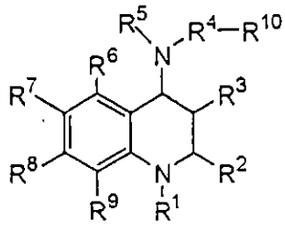
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester;

(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(morpholin-4-yl)pyridin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxy-2-methylpropyl ester;

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester; and

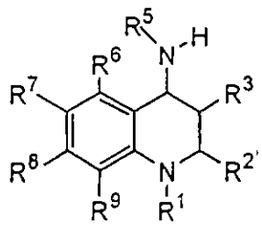
(2R,4S)-4-{(3-Cyano-5-trifluoromethylbenzyl)-[5-(2-methoxyethoxy)pyrimidin-2-yl]}amino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-carboxyethyl ester.

18. A process for preparing a tetrahydroquinoline derivative of the formula (I):



(I)

wherein the symbols R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} have the same meaning as defined in claim 1, which comprises condensing a compound of the formula (II):



(II)

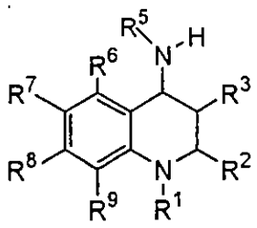
wherein each symbol has the same meaning as defined above with a

compound of the formula (III):

$R^{10}-R^4-Z^1$ (III)

wherein Z^1 is a leaving group and the other symbols have the same meaning as defined above.

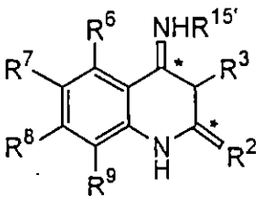
19. A compound of the formula (II):



(II)

wherein the symbols R^1, R^2, R^3, R^5, R^6, R^7, R^8 and R^9 have the same meaning as defined in claim 1, or a salt thereof.

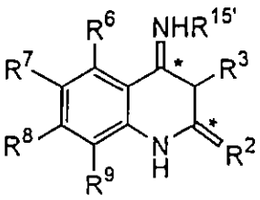
20. A diastereomer mixture of the formula (XIII-a):



(XIII-a)

wherein $R^{15'}$ is an optically active protecting group for amino group and the symbols R^2, R^3, R^6, R^7, R^8 and R^9 have the same meaning as defined in claim 1, or a salt thereof.

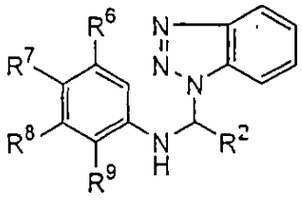
21. A process for preparing a diastereomer mixture of the formula (XIII-a):



(XIII-a)

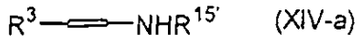
wherein $R^{15'}$ is an optically active protecting group for amino group and the symbols R^2, R^3, R^6, R^7, R^8 and R^9 have the same meaning as defined in

claim 1, which comprises reacting a compound of the formula (XV):



(XV)

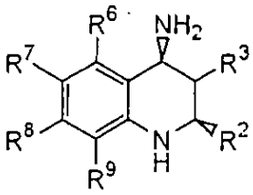
wherein each symbol has the same meaning as defined above with a compound of the formula (XIV-a):



(XIV-a)

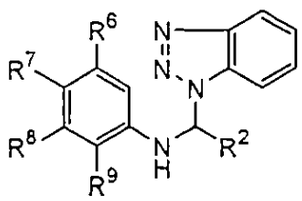
wherein each symbol has the same meaning as defined above.

22. A process for preparing an optically active compound of the formula (XIII-b)



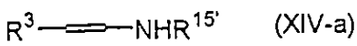
(XIII-b)

wherein the symbols R^2, R^3, R^6, R^7, R^8 and R^9 have the same meaning as defined in claim 1, which comprises reacting a compound of the formula (XV):



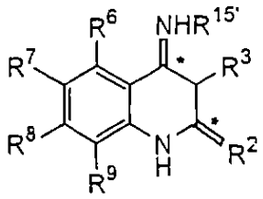
(XV)

wherein each symbol has the same meaning as defined above with a compound of the formula (XIV-a):



(XIV-a)

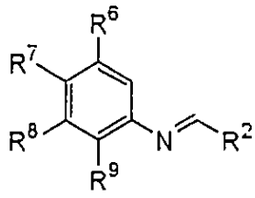
wherein $R^{15'}$ is an optically active protecting group for amino group and R^3 has the same meaning as defined above, resolving the resulting diastereomer mixture of the formula (XIII−a):



(XIII-a)

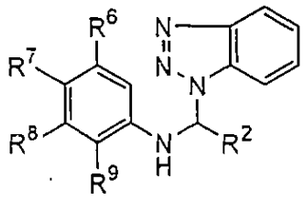
wherein each symbol has the same meaning as defined above, and removing the optically active protecting group for amino group.

23. The process of claim 21 or 22, wherein a compound of the formula (XVIII):



(XVIII)

wherein the symbols R^2, R^6, R^7, R^8 and R^9 have the same meaning as defined in claim 1 is used in place of the compound (XV):



(XV)

wherein each symbol has the same meaning as defined above.

24. A pharmaceutical composition, which comprises as an active ingredient a compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof.

25. A method for prophylaxis or treatment of arteriosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesteremia, hypertriglyceridemia, familial-hypercholesteremia, cardiovascular diseases, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, restenosis after angioplasty, hypertension, cerebral infarction, cerebral stroke, diabetes, vascular complication of diabetes, thrombotic diseases, obesity or endotoxemia, which comprises administering an effective

amount of a compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

26. Use of a compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, in treatment of patients suffering from arteriosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesteremia, hypertriglyceridemia, familial-hypercholesteremia, cardiovascular diseases, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, restenosis after angioplasty, hypertension, cerebral infarction, cerebral stroke, diabetes, vascular complication of diabetes, thrombotic diseases, obesity or endotoxemia.

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(71) Applicant (*for all designated States except US*): **TANABE SEIYAKU CO., LTD.** [JP/JP] 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP)

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **KUBOTA, Hitoshi** [JP/JP], c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi Osaka 5418505 (JP). **SUGAHARA, Masakatsu** [JP/JP], c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku Osaka-shi, Osaka, 5418505 (JP) **FURUKAWA, Mariko** [JP/JP], c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku Osaka-shi, Osaka, 5418505 (JP) **TAKANO, Mayumi** [JP/JP], c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 5418505 (JP) **MOTOMURA, Daisuke** [JP/JP], c/o TANABE SEIYAKU CO., LTD., 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka-shi Osaka, 5418505 (JP)

(74) Agents: **KAWAMIYA, Osamu** et al., AOYAMA & PARTNERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 5400001 (JP)

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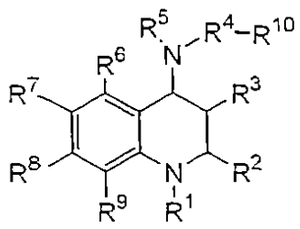
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(54) Title: TETRAHYDROQUINOLINE DERIVATIVES AND A PROCESS FOR PREPARING THE SAME



(I)

(57) Abstract: A novel compound of the formula (I) wherein R^1 is alkoxycarbonyl or the like; R^2 is alkyl or the like; R^3 is hydrogen or the like, R^4 is alkylene or the like, R^5 is optionally substituted heterocyclic group; R^6, R^7, R^8 and R^9 are independently hydrogen, alkyl, alkoxy or the like; R^{10} is optionally substituted aromatic ring, or the like; or a pharmaceutically acceptable salt thereof which has an inhibitory activity against cholesteryl ester transfer protein (CETP)

WO 2005/095409 A3

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/JP2005/006894

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A. CLASSIFICATION OF SUBJECT MATTER
C07D491/04 C07D401/14 C07D401/04 A61K31/47 A61K31/4545
A61K31/444 A61K31/4439 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document with indication where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/17165 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MAGNUS-ARYITEY, GEORGE, T) 30 March 2000 (2000-03-30) cited in the application page 1, line 4 - page 1, line 11; claims; examples 1-95	1-19, 24-26
A	WO 00/17166 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MULARSKI, CHRISTIAN, JAME) 30 March 2000 (2000-03-30) cited in the application page 1, line 4 - page 1, line 1; claims 1-34; examples 1-116	1-19, 24-26
X	FR 2 763 590 A (SYNTHELABO) 27 November 1998 (1998-11-27) page 15, example 24	20

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[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 2005	08. 12. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Schmid, A

Form PCT/ISA/210 (second sheet) (January 2004)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2005/006894

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 [X] Claims Nos..
because they relate to subject matter not required to be searched by this Authority, namely

Although claims 25 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2 [ ] Claims Nos.
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically

3 [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos..

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest

[X] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP2005/006894

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DERIVADOS DE TETRAHIDROQUINOLINA Y UN PROCEDIMIENTO PARA PREPARAR LOS MISMOS

CAMPO TÉCNICO

La presente invención se refiere a un nuevo derivado de tetrahidroquinolina que posee actividad inhibitoria contra la proteína de transferencia de colesteril éster (CETP).

TÉCNICA ANTERIOR

La hipercolesterolemia, especialmente el nivel elevado en suero de lipoproteina de colesterol de baja densidad (LDL), ha sido descubierta que es un factor de riesgo de enfermedades de arterioesclerosis por varios estudios epidemiológicos. Realmente, las drogas capaces de disminuir el nivel de colesterol LDL tal como inhibidores de reductasa 3-hidroxi-3-metilglutaril-CoA (HMG-CoA) han sido usadas con el objetivo de prevenir enfermedades de arteria coronaria, y demostraron poseer algunos beneficios en muchas pruebas clínicas a gran escala. Sin embargo, su efecto preventivo en enfermedades coronarias está limitado en alguna magnitud, y aún no es suficientemente satisfactorio.

Recientemente, se ha descubierto que el nivel bajo de lipoproteina de colesterol de alta densidad en suero (HDL) es un potente factor de riesgo en enfermedades de arterioesclerosis por diversos estudios epidemiológicos y pruebas clínicas a gran escala. El HDL es conocido por tener varios efectos antiarterioscleróticos y se enfoca la atención

en la potencialidad de drogas para aumentar el nivel de Colesterol HDL como un medio para prevención o tratamiento de enfermedades de arterioesclerosis. Sin embargo, no hay ninguna droga que pueda usarse de manera satisfactoria para este propósito. Los fibratos e inhibidores de HMG-CoA reductasa sólo tienen baja actividad de aumento del nivel de colesterol HDL; los derivados del ácido nicotínico pueden aumentar HDL significativamente, pero tienen serios problemas de tolerancia. Consiguientemente, hay una demanda de un agente que sea bien tolerado y que pueda elevar significativamente el nivel de colesterol HDL, previniendo o revirtiendo por esto la progresión de la ateroesclerosis.

Es conocido que muchas proteínas están involucradas en el mecanismo de la regulación del catabolismo de varias lipoproteinas. Entre éstas, el papel de la proteína de transferencia de colesteril éster (CETP) comenzó a llamar la atención. La CETP es una proteína responsable de la transferencia de colesteril éster (CE) y triglicérido entre lipoproteinas, y media en la transferencia de CE desde HDL a LDL o a lipoproteina de muy baja densidad (VLDL). Consiguientemente, la actividad de CETP afecta en gran medida la composición de lípidos en las partículas de lipoproteina. Por ejemplo, se conoce que la administración de un anticuerpo monoclonal de neutralización a CETP al conejo o hámster aumenta el nivel de colesterol HDL y hace disminuir el nivel

de colesterol LDL. Adicionalmente, el ser humano que posee actividad disminuida o eliminada de CETP debido a mutación del gen demuestra un aumento del nivel de colesterol HDL en sangre y disminuye el nivel de colesterol LDL en sangre. Por otra parte, se sabe que los ratones y ratas transgénicos realizados para expresar CETP demuestran disminución de nivel de colesterol HDL y aumento del nivel de colesterol LDL. Así, se considera que el CETP contribuye en gran medida a la regulación de lípido en suero, y por eso afecta el cambio de perfil de lípido en suero tal como la disminución de nivel de Colesterol HDL y aumento de Colesterol LDL. Consiguientemente, se supone que un valor elevado de actividad CETP induciría a la arterioesclerosis.

En realidad, la actividad de CETP varía, dependiendo de las especies animales. Es conocido que, las lesiones de arterioesclerosis son formadas fácilmente por carga de colesterol en los animales con actividad CETP aumentada tal como los conejos, se considera que tales lesiones apenas ocurren en animales con baja actividad CETP tal como las ratas. Además, se ha confirmado que la supresión continua de actividad de CETP por administración de oligodesoxinucleótido de sentido contrario produce efectos tales como aumento del nivel de colesterol HDL en sangre y reducción de lesiones de arteriosclerosis en un conejos alimentados con colesterol.

Los hallazgos anteriores indican que esta actividad de

CETP está en correlación negativa con el colesterol HDL, y esa inhibición de actividad de CETP disminuiría el grado de riesgo de enfermedades de arteriosclerosis. Se espera por consiguiente que los compuestos capaces de inhibir la actividad de CETP puedan bloquear la transferencia de colesterol HDL al LDL, y por esto incrementa el colesterol HDL el cual tiende a prevenir la arteriosclerosis mientras disminuye el colesterol LDL el cual tiende a promover la arterioesclerosis. De esta manera, tales compuestos pueden servir como un agente preventivo o terapéutico útil contra enfermedades de arterioesclerosis, hiperlipidemia o dislipidemia y pueden proveer por primera vez un tratamiento médico eficaz.

Los ejemplos de compuestos que tienen actividad inhibitoria de CETP incluyen los derivados de tetrahidroquinolina. Ver, WO00/17164, WO00/17165, WO00/17166.

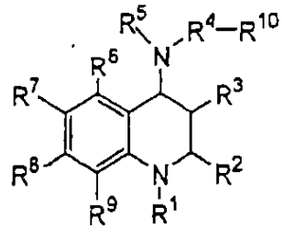
Sin embargo, estos compuestos tienen defectos. Es decir, los mismos son pobremente solubles en agua y no pueden ser absorbidos lo suficiente en el ser vivo, un nivel sanguíneo suficiente para alcanzar el efecto medicinal apenas puede lograrse inclusive cuando son administrados como una formulación convencional para administración oral. Ver, WO03/63868.

Consiguientemente, son muy solicitados compuestos nuevos en los cuales se han resuelto los defectos inidcados

precedentemente.

DESCRIPCIÓN DE LA INVENCIÓN

La presente invención provee derivados tetrahidroquinolina novedosos que poseen una excelente actividad inhibitoria de CETP en donde se han corregido los defectos de los compuestos inhibitorios de CETP existentes. Así, la presente invención provee un compuesto de la fórmula (I):



(I)

en donde R^1 es un átomo de hidrógeno, un grupo alcoxicarbonilo opcionalmente sustituido, un grupo carbamoilo opcionalmente sustituido, un grupo alquilo opcionalmente sustituido, un grupo alcanoilo opcionalmente sustituido, un grupo monocíclico o heterocíclico bicíclico saturados o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (grupo heterocíclico opcionalmente sustituido), o un grupo carbonilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (grupo heterocíclico opcionalmente sustituido);

R^2 es un átomo de hidrógeno o un grupo alquilo

opcionalmente sustituido;

R^3 es un átomo de hidrógeno o un grupo alquilo opcionalmente sustituido;

R^4 es un grupo alquileno opcionalmente sustituido;

R^5 es un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomoos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno, en donde el grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes, o dicho grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes y además por un átomo halógeno, un grupo oxo y/o hidroxilo:

grupo ciano, grupo nitro, grupo carboxilo, grupo sulfo, grupo alquilo C_{3-10}, grupo alquilo sustituido, grupo cicloalquilo opcionalmente sustituido, grupo alquenilo opcionalmente sustituido, grupo alcoxilo C_{3-10}, grupo alcoxilo sustituido, grupo cicloalcoxilo opcionalmente sustituido, grupo alcoxicarbonilo opcionalmente sustituido, grupo carbamoilo opcionalmente sustituido, grupo carbamimidoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, grupo alquilsulfinilo opcionalmente sustituido, grupo alquilsulfonilo opcionalmente sustituido, grupo amino opcionalmente sustituido, grupo sulfamoilo opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido,

grupo monociclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (grupo heterocíclico opcionalmente sustituido), un grupo oxilo monocíclico o heterocíclico bicíclico saturados o no saturado que contiene 1 a 4 heteroátomos seleccionados independientemente de átomos de oxígeno, azufre y nitrógeno (grupo oxilo heterocíclico es opcionalmente sustituido), y un grupo carbonilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (grupo carbonilo heterociclico es opcionalmente sustituido);

R^6, R^7, R^8 y R^9 son independientemente un átomo de hidrógeno, un átomo halógeno, un grupo hidroxilo, un grupo nitro, un grupo ciano, un grupo alquilo opcionalmente sustituido, un grupo alcoxilo opcionalmente sustituido, un grupo alquilsulfoniloxilo opcionalmente sustituido o un grupo amino opcionalmente sustituido; o

R^6 y R^7, ó R^7 y R^8, ó R^8 y R^9 pueden combinarse en los extremos para formar un grupo alquileno cuyo grupo alquileno puede contener 1 a 3 heteroátomos independientemente seleccionados de los átomos de nitrógeno, azufre y oxígeno, y puede tener sustituyente(s); y

R^{10} es un anillo aromático que contiene opcionalmente 1 a 3 heteroátomos independientemente seleccionados de átcmos de oxigeno, azufre y nitrógeno (el anillo aromático es opcionalmente sustituido), o una sal farmacéuticamente aceptable del mismo.

El compuesto (I) de la presente invención abarca una mezcla de estereoisómeros, estereoisómeros respectivos en una forma purificada o sustancialmente purificada. Por ejemplo, los compuestos de la fórmula (1) pueden tener uno o más átomos de carbono asimétricos y por consiguiente pueden concurrir como enantiómeros o diaestereómeros individuales, o una mezcla de los mismos. Los presentes compuestos incluyen isómeros respectivos y una mezcla de los mismos. Adicionalmente a lo anterior, cuando el compuesto (1) tiene un enlace doble, los isómeros geométricos pueden concurrir (en formas cis- y trans-), y cuando el compuesto (I) tiene un grupo que contiene un enlace no saturado tal como carbonilo, pueden ocurrir las formas tautoméricas, y los presentes compuestos incluyen isómeros respectivos y una mezcla de los mismos.

Además, las sales farmacéuticamente aceptables del compuesto (I) de la presente invención incluyen una sal intramolecular, un hidrato, solvato, o lo similar.

Tal como se utiliza en la presente, el término "anillo aromático que contiene opcionalmente 1 a 3 heteroátomos

independientemente seleccionado de los átomos de oxígeno, azufre y nitrógeno" preferentemente se refiere a un "anillo aromático monocíclico de 5 a 7 miembros que contiene opcionalmente 1 a 3 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno" que incluye específicamente grupo fenilo, furilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, azepinilo, oxepinilo y tiepinilo, y lo similar.

El término "grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de los átomos de oxígeno, azufre y nitrógeno" preferentemente se refiere a un grupo heterocíclico saturado o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno" que incluye específicamente los grupos siguientes. Los ejemplos de grupo heterocíclico de 5 miembros incluyen grupos 2H-pirrolilo, 3H-pirrolilo, 2-pirrolilo, 3-pirrolilo, pirrolidinilo, 1,3-dioxolanilo, oxazolilo, oxazolinilo, oxazolidinilo, tiazolilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, 2-pirazolinilo, pirazolidinilo, isoxazolilo, isotiazolilo, tetrazolilo, 1,2-ditiolilo, 1,3-ditiolilo, 3H-1,2-oxatiolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo,

1,3,4-oxadiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,3,4-tiadiazolilo, 1,2,3,4-oxatriazolilo, 1,2,3,5-oxatriazolilo, 3H-1,2,3-dioxazolilo, 1,2,4-dioxazolilo, 1,3,2-dioxazolilo, 1,3,4-dioxazolilo, 5H-1,2,5-oxatiazclilo y 1,3-oxatiolilo, y lo similar.

Los ejemplos de grupo heterocíclico de 6 miembros incluyen grupos 2H-piranilo, 4H-piranilo, piridilo, piperidinilo, 1,2-dioxinilo, 1,3-dioxinilo, 1,4-dioxanilo, morfolinilo, 1,4-ditianilo, tiomorfolinilo, piridazinilo, pirimidinilo, pirazinilo, piperazinilo, 1,3,5-triazinilo, 1,2,4-triazinilo, 1,2,3-triazinilo, 1,3,5-tritianilo, 4H-1,2-oxazinilo, 2H-1,3-oxazinilo, 6H-1,3-oxazinilo, 6H-1,2-oxazinilo, 1,4-oxazinilo, 2H-1,2-oxazinilo, 4H-1,4-oxazinilo, 1,2,5-oxatiazinilo, 1,4-oxazinilo, o-isoxazinilo, p-isoxazinilo, 1,2,5-ozatiazinilo, 1,2,6-oxathiazinilo, 1,4,2-oxadiazinilo y 1,3,5,2-oxadiazinilo, y lo similar.

Los ejemplos de grupo heterocíclico de 7 miembros incluyen grupo azepinilo, oxepinilo y tiepinilo, y lo similar.

Los ejemplos de grupo heterociclico de 8 miembros incluyen grupo azocinilo, oxocinilo y tiocinilo, y lo similar.

Tal como se utiliza en la presente, la fracción heterocíclico del "grupo oxilo monocíclico o heterociclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno", "grupo carbonilo monocíclico o

bicíclico heterocíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionado de átomos de oxígeno, azufre y nitrógeno", y "un grupo carbonilamino monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionado de los átomos de oxígeno, azufre y nitrógeno" se refiere al grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 hetercátomos independientemente seleccionado de átomos de oxígeno, azufre y nitrógeno" mencionado precedentemente.

En casos en donde la posición de enlace para este anillo aromático, grupo heterocíclico, y lo similar no está definida específicamente, la definición implica abarcar todas las posibles posiciones de enlace. Por ejemplo, el término "grupo piridilo" significa grupo 2-, 3- ó 4-piridilo, y el término que "grupo tienilo" significa grupo 2- ó 3-tienilo. El mismo se aplica a otros anillos aromáticos y grupos heterocíclicos.

Cuando el grupo monocíclico o heterocíclico bicíclico saturado o no saturado, grupo oxilo heterocíclico, grupo carbonilo heterocíclico y grupo carbonilamino heterocíclico cada uno conteniendo 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno tienen un sustituyente(s), la sustitución incluye oxidación de heteroátomo(s) en el heterociclo en los grupos respectivos. Específicamente, compuestos que tienen heteroátomo(s) en el

heterociclo de dichos grupos como N-óxido, S-óxido (SO) ó S,S-dióxido (SO_2) también se encuentran dentro del alcance de la presente invención.

El término "halógeno" se refiere al flúor, cloro, bromo o iodo.

El término "grupo alquilo" o "alquilo" significa un hidrocarburo saturado de cadena lineal o ramificada que tiene 1 a 10 átomos de carbono y una cadena de hidrocarburo saturada cíclica que tiene 3 a 10 átomos de carbono. Como el hidrocarburo de cadena de lineal o ramificada, son preferibles aquéllos que tienen 2 a 10 átomos de carbono y son más preferibles aquéllos que tienen 2 a 6 carbono. Otros ejemplos preferibles son los grupos alquilo de cadena lineal que poseen 1 a 6 átomos de carbono, especialmente aquéllos que tienen 1 a 4 átomos de carbono. Los ejemplos de grupo alquilo incluyen grupo metilo, etilo, propilo, isopropilo, butilo, sec-butilo, tert-butilo, pentilo, isopentilo, neopentilo, terc-pentilo, 1-metilbutilo, 2-metilbutilo, 3-metilbutilo, hexilo y isohexilo, y lo similar.

El término "grupo alcoxilo" o "alcoxilo" significa un grupo alquiloxilo lineal o ramificado que posee 1 a 10 átomos de carbono y un grupo alquiloxilo cíclico que posee 3 a 10 átomos de carbono. Como cadena de hidrocarburo lineal o ramificada, son preferibles aquéllas que tienen 2 a 10 átomos de carbono y son más preferibles aquéllas que tienen 2 a 6

átomos de carbono. Otros ejemplos preferibles son los grupos alcoxilo de cadena lineal que poseen 1 a 6 átomos de carbono, especialmente aquéllos que tienen 1 a 4 átomos de carbono. Los ejemplos de grupo alcoxilo incluyen grupo metoxilo, etoxilo, propoxilo, isopropoxilo, butoxilo, isobutoxilo, terc-butoxilo, pentoxilo, isopentoxilo, neopentoxilo, terc-pentoxilo, hexoxilo y isohexoxilo, y lo similar.

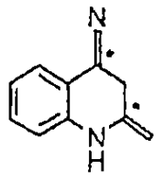
El término "grupo alquileno" o "alquileno" significa una cadena de hidrocarburo saturada en donde un átomo de hidrógeno es eliminado de cada uno de los carbonos terminales de una cadena de hidrocarburo lineal. Los ejemplos preferidos incluyen un grupo alquileno que tiene 1 a 6 átomos de carbono, específicamente, grupo metileno, etileno, trimetileno y tetrametileno, y lo similar. Cuando un grupo alquileno utilizado en la presente contiene 1 a 3 heteroátomos independientemente seleccionados de los átomos de nitrógeno, azufre y oxígeno, el término "alquileno" incluye un grupo de la fórmula: $-O-(CH_2)_m-O-$, $-S-(CH_2)_m-S-$, $-NH-(CH_2)_mNH-$, ó $-O-(CH_2)_m-NH-$ (en donde m es un entero de valor 1 a 4), o lo similar.

El término "gruupo alcanoilo" o "alcanoilo" significa un grupo alquilcarbonilo lineal o ramificado que posee 1 a 10 átomos de carbono, preferentemente un grupo alquilcarbonilo que tiene 1 a 6 átomos de carbono, más preferentemente un grupo alquilcarbonilo que tiene 1 a 4 átomos de carbono. Los

ejemplos de grupo alcanoilo incluyen grupo acetilo, propionilo, butirilo, valerilo y pivaloilo, y lo similar.

El término los "grupo alquenilo" o "alquenilo" significa una cadena de hidrocarburo lineal o ramificada que posee 2 a 10 átomos de carbono y contiene por lo menos un enlace doble, preferentemente un grupo alquenilo que tiene 2 a 6 átomos de carbono, más preferentemente un grupo alquenilo que tiene 2 a 4 átomos de carbono. Los ejemplos de grupo alquenilo incluyen grupo vinilo; 1-propenilo, alilo, isopropenilo, butenilo, butadienilo y pentenilo, y lo similar.

Tal como se utiliza en la totalidad de las presentes reivindicaiones y descripción, cuando el término "mono- o di-alquilo" se refiere a di-alquilo, las fracciones alquilo pueden ser independientes entre sí. Adicionalmente, un compuesto de fórmula siguiente significa que toma la configuración (2R*,4S*), cuando (2R*,4S*) indica una mezcla de (2R,4S) y (2S,4R).



Los compuestos de la presente invención tienen actividad inhibitoria de CETP y son eficaces para incrementar el colesterol HDL y disminuir el colesterol LDL. Consiguientemente, los compuestos son útiles para la prevención y/o tratamiento de enfermedades tales como la

arteriosclerosis, hiperlipidemia, y lo similar.

MEJOR MODALIDAD PARA REALIZACIÓN DE LA INVENCIÓN

Los compuestos preferidos de la presente invención son aquéllos en donde R^5 es un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno, en donde el grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes, o dicho grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes junto con átomo halógeno, grupo oxo y/o hidroxilo:

grupo ciano, grupo nitro, grupo carboxilo, grupo sulfo, grupo alquilo C_{3-10}, grupo alquilo sustituido, grupo cicloalquilo opcionalmente sustituido, grupo alquenilo opcionalmente sustituido, grupo alcoxilo C_{3-10}, grupo alcoxilo sustituido, grupo cicloalcoxilo opcionalmente sustituido, grupo alcoxicarbonilo opcionalmente sustituido, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido, grupo carbamidoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, grupo alquilsulfinilo opcionalmente sustituido, grupo alquilsulfonilo opcionalmente sustituido, grupo amino, grupo mono- o dialquilamino opcionalmente sustituido, grupo alcanoilamino opcionalmente sustituido, grupo

alcoxicarbonilamino opcionalmente sustituido, grupo alquilsulfonilamino opcionalmente sustituido, grupo mono- o di-alquilcarbamoilamino opcionalmente sustituido, un grupo carbonilamino monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (grupo carbonilamino heterocíclico es opcionalmente sustituido), grupo sulfamoilo, grupo mono o di-alquil sulfamoilo opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (grupo heterocíclico opcionalmente sustituido), un grupo oxilo monocíclico o heterocíclico bicíclico saturados o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno (el grupo oxilo heterocíclico es opcionalmente sustituido), y un grupo carbonilo monocíclico o bicíclico heterocíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo carbonilo heterocíclico es opcionalmente sustituido); y

R^{10} es un anillo aromático que contiene opcionalmente 1 a 3 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno, cuyo anillo aromático es opcionalmente sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes: átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo opcionalmente sustituido, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido, grupo alquilo opcionalmente sustituido, grupo alcoxilo opcionalmente sustituido, grupo hidroxilo, grupo nitro, grupo ciano, grupo amino, grupo mono- o dialquilamino opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, y un grupo monocíclico o heterociclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo heterocíclico es opcionalmente sustituido).

El (los) sustituyente(s) para grupo alquilo sustituido, grupo alquilo opcionalmente sustituido, grupo cicloalquilo opcionalmente sustituido, grupo alquenilo opcionalmente sustituido, grupo alcoxilo sustituido, grupo alcoxilo opcionalmente sustituido, grupo cicloalcoxilo opcionalmente sustituido, grupo alcoxicarbonilo opcionalmente sustituido, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, grupo

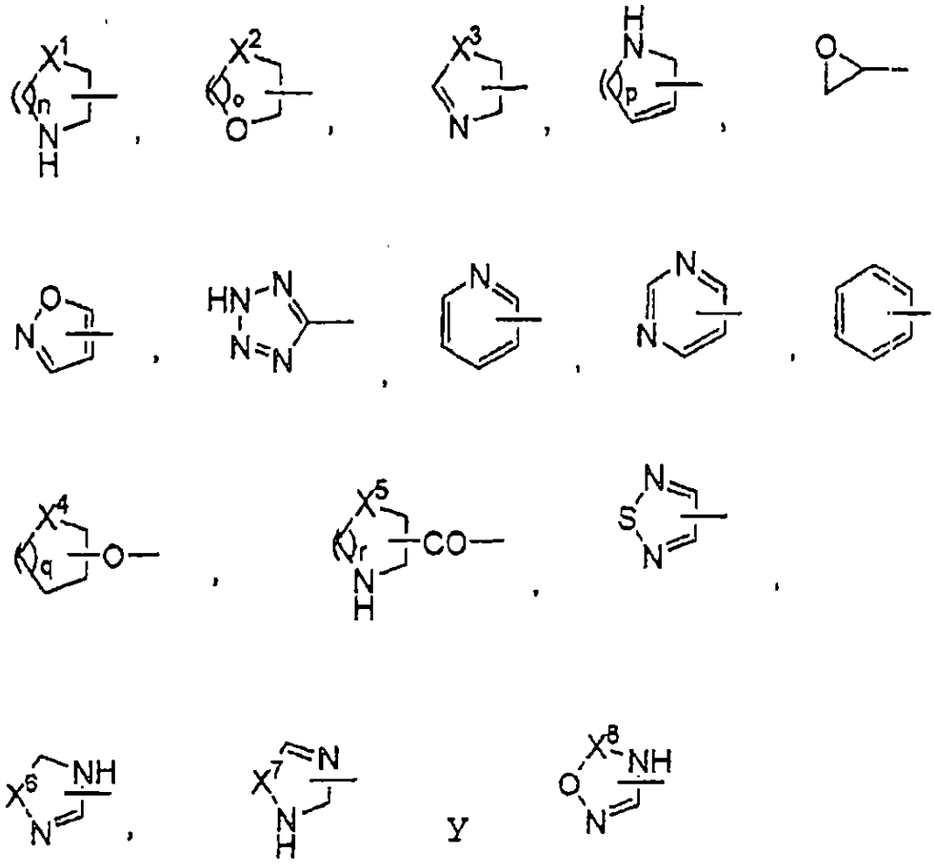
alquilsulfinilo opcionalmente sustituido, grupo alquilsulfonilo opcionalmente sustituido, grupo mono- o di-alquilamino opcionalmente sustituido, grupo alcanoilamino opcionalmente sustituido, grupo alcoxicarbonilamino opcionalmente sustituido, grupo alquilsulfonilamino opcionalmente sustituido, grupo mono- o di-alquilcarbamoilamino opcionalmente sustituido, grupo mono- o di-alquilsulfamoilo opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, grupo alquileno opcionalmente sustituido, un grupo carbonilamino monocíclico o heterocíclico biciclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionado de átomos de oxígeno, azufre y nitrógeno (el grupo de carbonilamino heterocíclico es opcionalmente sustituido), un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo heterocíclico opcionalmente sustituido), un grupo oxilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo oxilo heterocíclico es opcionalmente sustituido), y un grupo carbonilo monocíclico o heterocíclico bicíclico saturados o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre

y nitrógeno (el grupo carbonilo heterocíclico es opcionalmente sustituido) puede ser 1-5 grupos seleccionados de los grupos siguientes:

átomo halógeno; grupo ciano; grupo hidroxilo; grupo nitro; grupo carboxilo; grupo oxo; grupo tioxo; grupo sulfo; grupo cicloalquilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o dialquilamino, grupo fenilo o grupo morfolinilo; grupo alcoxicarbonilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo carbamoilo; grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alquilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alcanoilo opcionalmente sustituido por hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alcoxilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo

alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o morfolinilo; grupo alcanoiloxilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alquiltio opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alquilsulfonilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alquilsulfinilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo mono- o di-alquilsulfamoilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo amino; grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo mono- o di-alquilsulfamoilamino opcionalmente sustituido por grupo

hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo mono- o di-alquilureido opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; y un grupo de la fórmulas:



en donde X^1 y X^3 son independientemente CH_2, NH, O, S, SO o SO_2; X^2 y X^5 son independientemente CH_2, O, S, SO o SO_2; X^4 es NH, O, S, SO o SO_2; X^6 y X^7 son independientemente O ó S; X^8 es S ó SO; y n, o, p, q y r son

independientemente un entero de valor 1 a 4, en donde cada de grupo de la fórmula anterior es opcionalmente sustituido por 1 a 3 sustituyentes seleccionados de los grupos siguientes:

átomo halógeno, grupo carboxilo, grupo hidroxilo. grupo ciano, grupo oxo, los tioxo grupo, grupo alquilo, grupo hidroxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialquilo, grupo morfolinilalquilo, grupo fenilalquilo, grupo alcanoilo, grupo hidroxialcanoilo, grupo alcoxialcanoilo, grupo alcoxilo, grupo fenilalcoxilo, grupo alcoxicarbonilo, grupo benciloxicarbonilo, grupo mono- o di-alquilamino, grupo mono- o di-alquilcarbamoilo, grupo mono- c di-alquilsulfamoilo, grupo alquilsulfonilo y grupo tetrazolilo.

Además, el "anillo aromático que opcionalmente contiene 1 a 3 heteroátomos independientemente seleccionados de los átomos de oxígeno, azufre y nitrógeno" es preferentemente un grupo fenilo, naftilo, piridilo, quinolilo, isoquinolilo, furilo, pirimidinilo, triazolilo o tienilo;

El "grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de los átomos de oxigeno, azufre y nitrógeno" es preferentemente un grupo morfolinilo, tiomorfolinilo, piperazinilo, pirrolidinilo, piperidinilo,

hexahidroazepinilo, pirrolinilo, imidazolidinilo, oxazolidinilo, tetrahidropiranilo, tetrahidrofuranilo, dioxolanilo, oxiranilo, pirimidinilo, piridilo, triazolilo, tetrazolilo, oxadiazolilo, dihidropirimidinilo, pirazinilo, tiazolilo, oxazolinilo, oxazolilo, piridazinilo, imidazolinilo, imidazolilo, pirazinilo, tienilo, pirrolilo, furilo ó dihidrooxazinilo.

El "grupo oxilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 hetercátomos independientemente seleccionados de los átomos de oxígeno, azufre y nitrógeno" es preferentemente un grupo morfoliniloxilo, tiomorfoliniloxilo, piperaziniloxilo, pirrolidiniloxilo, piperidiniloxilo, hexahidroazepiniloxilo, pirroliniloxilo, imidazolidiniloxilo, oxazolidiniloxilo, tetrahidropiraniloxilo, tetrahidrofuraniloxilo, dioxolaniloxilo, oxiraniloxilo, pirimidiniloxilo, piridiloxilo, triazoliloxilo, tetrazoliloxilo, oxadiazoliloxilo, dihidropirimidiniloxilo, pirazinıloxilo, tiazoliloxilo, oxazoliniloxilo, oxazoliloxilo, piridaziniloxilo, imidazoliniloxilo, imidazoliloxilo, piraziniloxilo, tieniloxilo, pirroliloxilo, furiloxılo o dihidrooxaziniloxilo.

El "grupo carbonilo monocíclico o bicíclico heterocíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de los átomos

de oxígeno, azufre y nitrógeno" es preferentemente un grupo morfolinilcarbonilo, tiomorfolinilcarbonilo, piperazinilcarbonilo, pirrolidinilcarbonilo, piperidinilcarbonilo, hexahidroazepinilcarbonilo, pirrolinilcarbonilo, imidazolidinilcarbonilo, oxazohdinilcarbonilo, tetrahidropiranilcarbonilo, tetrahidrofuranilcarbonilo, dioxolanilcarbonilo, oxiranilcarbonilo, pirimidinilcarbonilo, piridilcarbonilo, triazolilcarbonilo, tetrazolilcarbonilo, oxadiazolilcarbonilo, dihidropirimidinilcarbonilo, pirazinilcarbonilo, tiazolilcarbonilo, oxazolinilcarbonilo, oxazolilcarbonilo, piridazinilcarbonilo, imidazolinilcarbonilo, imidazolilcarbonilo, pirazinilcarbonilo, tienilcarbonilo, pirrolilcarbonilo, furilcarbonilo o dihidrooxazinilcarbonilo.

El "grupo carbonilamino monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de los átomos de oxígeno, azufre y nitrógeno" son preferentemente un grupo morfolinilcarbonilamino, tiomorfolinilcarbonilamino, piperazinilcarbonilamino, pirrolidinilcarbonilamino, piperidinilcarbonilamino, hexahidroazepinilcarbonilamino, pirrolinilcarbonilamino, imidazolidinilcarbonilamino, oxazolidinilcarbonilamino, tetrahidropiranilcarbonilamino, tetrahidrofuranilcarbonilamino, dioxolanilcarbonilamino, oxiranilcarbonilamino, pirimidinilcarbonilamino,

piridilcarbonilamino, triazolilcarbonilamino, tetrazolilcarbonilamino, oxadiazolilcarbonilamino, dihidropirimidinilcarbonilamino, pirazinilcarbonilamino, tiazolilcarbonilamino, oxazolinilcarbonilamino, oxazolilcarbonilamino, piridazinilcarbonilamino, imidazolinilcarbonilamino, imidazolilcarbonilamino, pirazinilcarbonilamino. tienilcarbonilamino, pirrolilcarbonilamino, furilcarbonilamino o dihidrooxazinilcarbonilamino.

En una modalidad de realización preferida de la presente invención, R^1 es un átomo de hidrógeno; un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo alquiltio, grupo alquilsulfonilo, grupo alquenilo, grupo amino, grupo mono- o di-alquilamino, grupo tetrazolilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo (dicho grupo mono o di-alquilcarbamoilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo

carboxilo y grupo alcoxicarbonilo), grupo alcanoilamino (dicho grupo alcanoilamino es opcionalmente sustituidc por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo hidroxilo y átomo halógeno), átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo morfolinilo opcionalmente sustituido por grupo oxo, grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo pirrolidinilo (dicho grupo

pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), y grupo pirimidinilo (dicho grupo pirimidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo); un grupo carbamoilo opcionalmente sustituido por grupo alcoxilo; grupo dihidrooxazolilo opcionalmente sustituido por 1 a 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; grupo dihidroimidazolilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; grupo dihidrooxazinilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; grupo mono- o

di-alquilcarbamoilo sustituido por 1 a 5 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- o di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo); un grupo alquilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono o di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo); un grupo alcanoilo opcionalmente

sustituido por 1 a 5 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- o di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo); un grupo morfolinilcarbonilo; un grupo piperazinilcarbonilo opcionalmente sustituido por grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilalquilo; un grupo pirrolidinilcarbonilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo; o un grupo piperidinilcarbonilo opcionalmente sustituido por 1 a 3 sustituyentes seleccionados independientemente del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo;

R^5 es un grupo heterocíclico saturado o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos

independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno;

en donde dicho grupo heterocíclico es sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes, o dicho grupo heterocíclico es sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes junto con un átomo halógeno, un grupo oxo y/o hidroxilo:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo cicloalquilo opcionalmente sustituido por carboxilo o grupo alcoxicarbonilo;

grupo alquilo C_{3-10};

grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo mono- o di-alquilcarbamoilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo fenilo, carboxilo o hidroxilo), grupo alcanoilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino opcionalmente sustituido por grupo carboxilo o alcoxilo, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo

oxiranilo, grupo dioxolanilo opcionalmente sustituido por grupo alquilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o grupo carboxilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo; grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo morfolinilo, y grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo;

grupo alquenilo opcionalmente sustituido por un grupo seleccionado de grupo ciano, grupo hidroxilo, grupo carboxilo, grupo benciloxicarbonilo, y grupo tetrazolilo;

grupo alqueniloxilo opcionalmente sustituido por grupo carboxilo;

grupo alcoxilo C_{3-10};

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo (dicho grupo mono- o di-alquilcarbamoilo es opcionalmente sustituido por grupo carboxilo, alcoxicarbonilo o hidroxilo), grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo carboxilo, formilo o hidroxilo), grupo alcanoiloxilo, grupo

alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo aminosulfonilo, grupo amino, grupo mono- o di-alquilamino sustituido por grupo carboxilo o alcoxilo, grupo mono o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo cicloalquilo opcionalmente sustituido por grupo carboximetilo, grupo oxiranilo, grupo fenilo opcionalmente sustituido por grupo alcoxilo o carboxilo, grupo morfolinilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o grupo carboxialquilo, grupo pirrolidinilo sustituido por grupo oxo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o grupo carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo pirimidinilo, grupo piridilo, grupo dioxolanilo opcionalmente sustituido por grupo alquilo, grupo oxadiazolilo opcionalmente sustituido por grupo oxo, grupo oxatiadiazolilo opcionalmente sustituido por grupo oxo, grupo pirrolidinilcarbonilo opcionalmente sustituido por grupo carboxilo, grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo, y grupo morfolinilcarbonilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo

fenilo;

grupo carbamoilo;

grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por un grupo seleccionado de grupo carboxilo, grupo morfolinilo y grupo alcoxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo y grupo mono- o di-alquilcarbamoilo; grupo alquilsulfinilo;

grupo alquilsulfonilo opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo y grupo mono- o di-alquilcarbamoilo;

grupo amino;

grupo mono- o di-alquilamino opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o grupo di-alquilamino y grupo morfolinilo;

grupo mono o di-alcanoilamino opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo alcoxilo, grupo carboxilo y grupo amino;

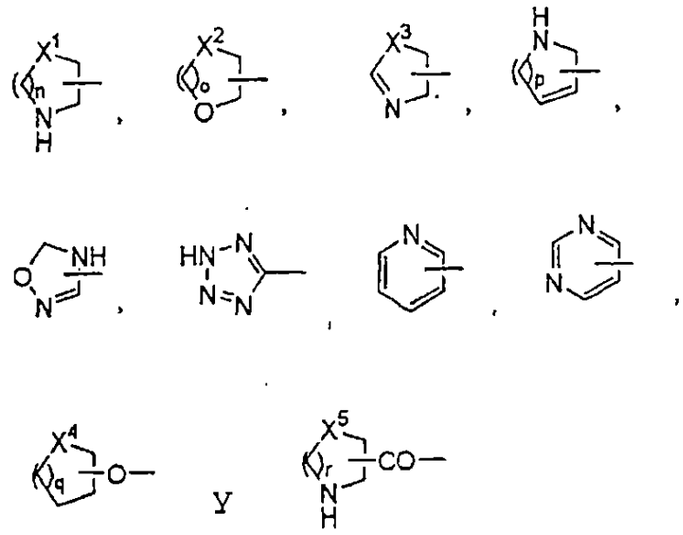
grupo mono- o di-alquilcarbamoilamino opcionalmente sustituido por grupo alcoxilo;

grupo morfolinilcarbonilamino;

grupo sulfamoilo;

grupo mono- o di-alquilsulfamoilo;

grupo alcanoilo opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino y grupo morfolinilo; o un grupo seleccionado de los grupos siguientes:



en donde X^1 y X^3 son independientemente CH_2, NH, O, S, SO ó SO_2; X^2 y X^5 son independientemente CH_2, O, S, SO ó SO_2; X^4 es NH, O, S, SO ó SO_2; y n, o, p, q y r son independientemente un entero de valor 1 a 4, en donde cada grupo de la fórmula anterior es opcionalmente sustituido por un(os) sustituyente(s) seleccionado(s) de los grupos siguientes:

grupo carboxilo, grupo hidroxilo, grupo ciano, grupo oxo, grupo alquilo, grupo hidroxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialquilo, grupo morfolinilalquilo, grupo fenilalquilo, grupo alcanoilo,

grupo hidroxialcanoilo, grupo alcoxialcanoilo, grupo alcoxilo, grupo fenilalcoxilo, grupo alcoxicarbonilo, grupo benciloxicarbonilo, grupo mono- o di-alquilamino, grupo mono- o di-alquilcarbamoilo, grupo mono- o di-alquilsulfamoilo, grupo alquilsulfonilo y grupo tetrazolilo;

R^6, R^7, R^8 y R^9 son independientemente un átomo de hidrógeno, un átomo halógeno, un grupo hidroxilo, un grupo nitro, un grupo ciano, un grupo alquilo, un grupo alcoxilo, o un grupo mono- o di-alquilamino, en donde dichos grupos alquilo, alcoxilo y mono- o di-alquilamino son opcionalmente sustituidos por 1 a 6 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo alcoxilo, grupo alquiltio, grupo amino, grupo nitro, grupo ciano, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo y grupo mono- o di-alquilamino; o

R^6 y R^7, ó R^7 y R^8, ó R^8 y R^9 pueden combinarse en los extremos para formar un grupo alquileno y dicho grupo alquileno puede contener 1 a 3 heteroátomos independientemente seleccionados de los átomos de nitrógeno, azufre y oxígeno;

R^{10} es un anillo monocíclico aromático que opcionalmente contiene 1 a 3 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno;

en donde el anillo monocíclico aromático es

opcionalmente sustituido por 1 a 4 sustituyentes independientemente seleccionados del átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo, grupo alquilo, grupo alcoxilo, grupo hidroxilo, grupo nitro, grupo ciano, grupo amino, grupo mono- o di-alquilamino, grupo alcanoilo, grupo alquiltio, grupo tetrazolilo y grupo dihidrooxazolilo, en donde los grupo alquilo, alcoxilo, mono- o di-alquilamino, mono- o dialquilcarbamoilo, alcanoilo y alquiltio son opcionalmente sustituidos por un sustituyente(s) independientemente seleccionado del átomo halógeno, y grupo hidroxilo, alcoxilo, amino, morfolinilo, piperidinilo, pirrolidinilo, piperazinilo, alquilpiperazinilo y alcanoilpiperazinilo.

Adicionalmente, en los compuestos preferidos, el "anillo monocíclico aromático que contiene opcionalmente 1 a 3 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno" es un grupo fenilo, un grupo piridilo, un grupo pirimidinilo, un grupo furilo o un grupo tienilo; y el "grupo heterocíclico saturado o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos independientemente seleccionados de los átomos de oxígeno, azufre y nitrógeno" es un grupo pirimidinilo, un grupo piridilo, un grupo triazolilo, un grupo tetrazolilo, un grupo oxadiazolilo, un grupo dihidropirimidinilo, un grupo

pirazinilo, un grupo tiazolilo, un grupo oxazolilo, un grupo imidazolilo, un grupo dihidrooxazinilo, un grupo dihidropirazinilo o un grupo pirazolilo.

En los compuestos más preferidos, R^1 es un átomo de hidrógeno; un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo alquiltio, grupo alquilsulfonilo, grupo alquenilo, grupo amino, grupo mono- o di-alquilamino, grupo tetrazolilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo (dicho grupo mono- o di-alquilcarbamoilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo y grupo alcoxicarbonilo), grupo alcanoilamino (dicho grupo alcanoilamino es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo hidroxilo y átomo halógeno), átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo

hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo morfolinilo opcionalmente sustituido por grupo oxo, grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo carboxialcoxilo, grupo alcoxicarbonilalcoxilo), grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), y grupo pirimidinilo (dicho grupo pirimidinilo es opcionalmente

sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo carboxialcoxilo, grupo alcoxicarbonilalcoxilo); grupo dihidrooxazolilo opcionalmente sustituido por 1 a 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; o un grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- o dialquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo);

R^2 es un grupo alquilo;

R^3 es un átomo de hidrógeno;

R^4 es un grupo alquileno;

R^5 es un grupo heterocíclico seleccionado de grupo

pirimidinilo, grupo piridilo, grupo triazolilo, grupo tetrazolilo, grupo oxadiazolilo, grupo dihidropirimidinilo, grupo pirazinilo, grupo tiazolilo, grupo oxazolilo, grupo imidazolilo, grupo dihidrooxazinilo, grupo pirazolilo y grupo dihidropirazinilo, en donde dicho grupo heterocíclico es sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes, ó 1 a 4 sustituyentes seleccionados de los grupos siguientes y grupo oxo:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo alquilo C_{3-10}; grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo mono- o di-alquilcarbamoilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo fenilo, carboxilo o hidroxilo), grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino opcionalmente sustituido por grupo carboxilo o alcoxilo, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo dioxolanilo opcionalmente sustituido por grupo alquilo, grupo pirrolidinilo opcionalmente sustituido

por grupo alcoxicarbonilo o carboxilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxualquilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo morfolinilo, y grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo; grupo alquenilo opcionalmente sustituido por un grupo seleccionado del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo benciloxicarbonilo, y grupo tetrazolilo;

grupo alqueniloxilo opcionalmente sustituido por grupo carboxilo;

grupo alcoxilo C_{3-10};

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo hidroxilo, grupo alcoxilo opcionalmente sustituido por grupo carboxilo o hidroxilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo aminosulfonilo, grupo amino, grupo mono- o di-alquilamino sustituido por grupo carboxilo o alcoxilo, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-

alquilureido opcionalmente sustituido por grupo morfolinilo, grupo cicloalquilo vsustituido por el grupo carboximetilo, grupo oxiranilo, grupo fenilo opcionalmente sustituido por grupo alcoxilo o carboxilo, grupo morfolinilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo pirrolidinilo opcionalmente sustituido por grupo oxo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo pirimidinilo, grupo piridilo, grupo dioxolanilo opcionalmente sustituido por grupo alquilo, grupo oxadiazolilo opcionalmente sustituido por grupo oxo, grupo oxatiadiazolilo opcionalmente sustituido por grupo oxo, grupo pirrolidinilcarbonilo opcionalmente sustituido por grupo carboxilo, grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo, y grupo morfolinilcarbonilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo fenilo;

grupo carbamoilo;

grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo seleccionado de grupo carboxilo, grupo

morfolinilo y grupo alcoxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo y grupo mono- o di-alquilcarbamoilo;

grupo alquilsulfinilo;

grupo alquilsulfonilo opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo y grupo mono- o di-alquilcarbamoilo;

grupo amino;

grupo mono- o di-alquilamino opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino y grupo morfolinilo; grupo alcanoilamino opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo alcoxilo, grupo carboxilo y grupo amino;

grupo mono- o di-alquilureido opcionalmente sustituido por grupo alcoxilo;

grupo morfolinilcarbonilamino;

grupo sulfamoilo;

grupo mono- o di-alquilsulfamoilo;

grupo morfolinilo opcionalmente sustituido por un grupo seleccionado del grupo oxo y grupo carboxilo;

grupo tiomorfolinilo opcionalmente oxidado;

grupo piperazinilo opcionalmente sustituido por un grupo

seleccionado del grupo ciano, grupo alquilo, grupo hidroxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialquilo, grupo alcanoilo, grupo hidroxialcanoilo, grupo alcoxialcanoilo, grupo benciloxicarbonilo, grupo mono- o di-alquil-carbamoilo, grupo mono- o di-alquilsulfamoilo, grupo alquilsulfonilo y grupo tetrazolilo;

grupo piperidinilo opcionalmente sustituido por un grupo seleccionado del grupo carboxilo, grupo hidroxilo, grupo oxo, grupo alquilo, grupo hidroxialquilo, grupo carboxialquilo, grupo alcanoilo, grupo alcoxilo, grupo fenilalcoxilo, grupo alcoxicarbonilo y grupo alcoxicarbonilalquilo;

grupo pirrolidinilo opcionalmente sustituido por un grupo seleccionado del grupo oxo, grupo carboxilo, grupo alcanoilo y grupo mono o di-alquilamino;

grupo pirrolinilo opcionalmente sustituido por grupo oxo; grupo hexahidrodiazepinilo opcionalmente sustituido por grupo alcanoilo; grupo diazolidinilo opcionalmente sustituido por grupo oxo;

grupo dioxolanilo opcionalmente sustituido por grupo alquilo;

grupo piridilo opcionalmente sustituido por grupo carboxilo, grupo hidroxilo o grupo hidroxialquilo (dicho grupo piridilo es opcionalmente oxidado adicionalmente);

grupo tetrazolilo opcionalmente sustituido por grupo hidroxilo o grupo alquilo que es sustituido por grupo

morfolinilo;

grupo dihidrooxadiazolilo opcionalmente sustituido por grupo oxo;

grupo dihidroimidazolilo;

grupo dihidrooxazolilo;

grupo oxazolidinilo opcionalmente sustituido por grupo oxo;

grupo tetrahidropiridilo opcionalmente sustituido por grupo bencilo;

grupo pirimidinilo;

grupo tetrahidropiranilo;

grupo piperidiniloxilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo carboxilo, grupo carboxialquilo y grupo alcanoilo;

grupo pirrolidiniloxilo sustituido opcionalmente por un grupo seleccionado del grupo alquilo, grupo carboxilo, grupo carboxialquilo y grupo alcanoilo;

grupo tetrahidropiraniloxilo;

grupo tetrahidrofuraniloxilo;

grupo tianiloxilo opcionalmente oxidado;

grupo morfolinilcarbonilo;

grupo piperazinilcarbonilo opcionalmente sustituido por un grupo seleccionado del grupo alcanoilo y grupo alquilo; y

grupo pirrolidinilcarbonilo;

R^6 y R^9 cada uno es un átomo de hidrógeno;

R^7 y R^8 son independientemente un átomo de hidrógeno, un grupo alquilo opcionalmente sustituido por átomo halógeno, un grupo alcoxilo, un grupo mono- o di-alquilamino o átomo halógeno; o

R^7 y R^8 se combinan en los extremos para formar un grupo alquilendioxilo; y

R^{10} es un grupo fenilo o piridilo, cuyo grupo fenilo o piridilo es opcionalmente sustituido por 1 a 4 sustituyentes seleccionados de grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, grupo hidroxilo, átomo halógeno, grupo ciano, grupo amino y grupo mono- o di-alquilamino.

En los compuestos preferidos adicionales, R^1 es un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo y grupo alcoxicarbonilo), de grupo alquenilo, átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo), grupo fenilo (dicho grupo

fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); y grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); o un grupo dihidrooxazolilo opcionalmente sustituido por 1 ó 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo;

R^5 es un grupo pirimidinilo, un grupo piridilo, un grupo triazolilo, un grupo tetrazolilo, un grupo oxadiazolilo, un grupo dihidropirimidinilo, un grupo pirazinilo, un grupo tiazolilo, un grupo oxazolilo, un grupo dihidrooxazinilo, un grupo pirazolilo o un grupo dihidropirazinilo, siendo dicho grupo sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo opcionalmente sustituido por grupo carboxilo o hidroxilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alquenilo opcionalmente sustituido por grupo carboxilo, grupo ciano o grupo benciloxicarbonilo;

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo opcionalmente sustituido por grupo carboxilo o hidroxilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo

alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo fenilo;

grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo carboxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio;

grupo alquilsulfinilo;

grupo alquilsulfonilo opcionalmente sustituido por grupo carboxilo;

grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino o grupo morfolinilo;

grupo mono- o di-alquilsulfamoilo;

grupo morfolinilo;

grupo tiomorfolinilo opcionalmente oxidado;

grupo piperazinilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo;

grupo piperidinilo opcionalmente sustituido por un grupo seleccionado del grupo carboxilo, grupo alquilo y grupo alcoxicarbonilo;

grupo dioxolanilo opcionalmente sustituido por grupo alquilo;

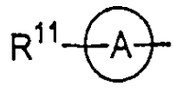
grupo tetrazolilo opcionalmente sustituido por grupo alquilo, grupo hidroxialquilo o grupo morfolinilalquilo;

grupo dihidrooxadiazolilo opcionalmente sustituido por grupo oxo; grupo pirimidinilo; o

grupo tetrahidropiranilo; y

R^{10} es un grupo fenilo o piridilo, siendo dicho grupo fenilo o piridilo opcionalmente sustituido por 1 a 4 sustituyentes seleccionados de grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, grupo hidroxilo, átomo halógeno, grupo ciano, grupo amino y grupo mono- o di-alquilamino.

Otra modalidad de realización de la presente invención incluye compuestos de la fórmula (I) en donde R^5 es un grupo de la fórmula:



en donde el anillo A es un grupo heterocíclico saturado

o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno, y.

R^{11} es un grupo seleccionado de los grupos siguientes:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo fenilo, hidroxilo o carboxilo), grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- c di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo , grupo oxiranilo, grupo dialquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alquenilo opcionalmente sustituido por grupo

carboxilo, grupo ciano o grupo benciloxicarbonilo;

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo; grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo fenilo, hidroxilo o carboxilo), grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo fenilo; grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo carboxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio;

grupo alquilsulfinilo;

grupo alquilsulfonilo opcionalmente sustituido por grupo carboxilo;

grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino o grupo morfolinilo;

grupo mono- o di-alquilsulfamoilo;

grupo morfolinilo;

grupo tiomorfolinilo opcionalmente oxidado;

grupo piperazinilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo;

grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo carboxialquilo, grupo alquilo, grupo alcoxicarbonilo o grupo alcoxicarbonilalquilo;

grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo carboxialquilo, grupo alquilo, grupo alcoxicarbonilo o grupo alcoxicarbonilalquilo;

grupo dioxolanilo opcionalmente sustituido por grupo alquilo;

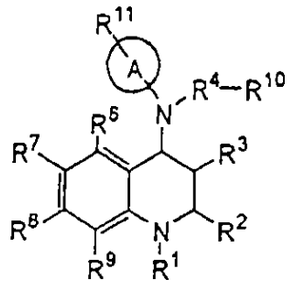
grupo tetrazolilo opcionalmente sustituido por grupo alquilo, grupo hidroxialquilo o grupo morfolinilalquilo;

grupo dihidrooxadiazolilo opcionalmente sustituido por grupo oxo;

grupo pirimidinilo; o

grupo tetrahidropiranilo;

cuyo compuesto se ilustra por la fórmula (I-A):



(I-A)

en donde cada simbolo posee el mismo significado como el definido anteriormente.

La modalidad de realización más preferida incluye compuestos de la fórmula (I) en donde R^1 es un átomo de hidrógeno; un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo alquiltio, grupo alquilsulfonilo, grupo alquenilo, grupo amino, grupo mono- o di-alquilamino, grupo tetrazolilo, grupo carbamoilo, (el grupo mono- o di-alquilcarbamoilo (dicho grupo mono- o diaiquilcarbamoilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo y grupo alcoxicarbonilo), grupo alcanoilamino (dicho grupo alcanoilamino es opcionalmente sustituido por 1

a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo hidroxilo y átomo halógeno), átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo morfolinilo opcionalmente sustituido por grupo oxo, grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo carboxialcoxilo, grupo alcoxicarbonilalcoxilo), grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo

hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), y grupo pirimidinilo (dicho grupo pirimidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo carboxialcoxilo, grupo alcoxicarbonilalcoxilo); grupo dihidrooxazolilo sustituido por 1 a 2 sustituyentes independientemente opcionalmente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; o un grupo mono- o di-alquilcarbamoilo sustituido por 1 a 5 sustituyentes independientemente seleccionados opcionalmente del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- o di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino

y grupo hidroxilo);

R^2 es un grupo alquilo;

R^3 es un átomo de hidrógeno;

R^4 es un grupo alquileno;

El anillo A y R^{11} son grupos iguales a los definidos precedentemente;

R^6 y R^9 cada uno es un átomo de hidrógeno;

R^7 y R^8 son independientemente un átomo de hidrógeno, un grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, o grupo mono- o di-alquilamino; o se combinan en los extremos para formar un grupo alquilendioxilo; y

R^{10} es un grupo fenilo o piridilo siendo dicho grupo fenilo o piridilo opcionalmente sustituido por 1 a 4 sustituyentes seleccionados del grupo alquilo opcionalmente sustiuido por átomo halógeno, grupo alcoxilo, grupo hidroxilo, átomo halógeno, grupo ciano, grupo amino y grupo mono- o di-alquilamino.

Otra modalidad de realización preferida incluye compuestos de la fórmula (I) en donde el anillo A es un grupo heterocíclico saturado o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno, y

R^{11} es un grupo seleccionado de los grupos siguientes: grupo ciano; grupo nitro; grupo carboxilo; grupo sulfo; grupo alquilo sustituido por un grupo seleccionado del átomo

halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo opcionalmente sustituido por grupo fenilo o hidroxilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o dialquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o dialquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo; grupo opcionalmente alquenilo sustituido por grupo carboxilo o grupo benciloxicarbonilo; grupo alcoxilo sustituido por grupo carboxilo, grupo hidroxilo, grupo alcoxilo, grupo alquiltio, grupo alquilsulfonilo o grupo alcoxifenilo; grupo alcoxicarbonilo vsustituido por grupo fenilo; grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo carboxilo; grupo hidroxicarbamimidoilo; grupo alquiltio; grupo alquilsulfinilo; grupo alquilsulfonilo opcionalmente sustituido por grupo alcoxicarbonilo; grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino o grupo morfolinilo; grupo mono- o di-alquilsulfamoilo; grupo morfolinilo; grupo tiomorfolinilo opcionalmente oxidado; grupo piperazinilo opcionalmente

sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo; grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo alquilo o grupo alcoxicarbonilo; grupo dioxolanilo opcionalmente sustituido por grupo alquilo; grupo tetrazolilo sustituido por grupo alquilo, grupo hidroxialquilo o grupo morfolinilalquilo; grupo dihidrooxadiazolilo opcionalmente sustituido por grupo oxo; grupo pirimidinilo; o grupo tetrahidropiranilo.

La modalidad de realización más preferida en la presente incluye compuestos de la fórmula (1) en donde R^1 es un grupo alcoxicarbonilo opcionalmente sustituido por un grupo seleccionado del grupo hidroxilo y grupo alcoxilo; o un grupo dihidrooxazolilo opcionalmente sustituido por grupo hidroxialquilo;

R^2 es un grupo alquilo;

R^3 es un átomo de hidrógeno;

R^4 es un grupo alquileno;

el anillo A y R^{11} son los mismos grupos como los definido anteriormente;

R^6 y R^9 cada uno es un átomo de hidrógeno; y

R^7 y R^8 son independientemente un átomo de hidrógeno, un grupo alquilo opcionalmente sustituidos por 1 a 9 átomos halógenos, un grupo alcoxilo, o un grupo mono- o di-alquilamino; o se combinan en los extremos para formar un

grupo alquilendioxilo;

R^{10} es un grupo fenilo o piridilo siendo dicho grupo fenilo o piridilo opcionalmente sustituido por 1 a 4 sustituyentes seleccionados del grupo alquilo opcionalmente sustiuidos por 1 a 9 átomos halógenos, grupo alcoxilo, grupo hidroxilo, átomo halógeno, grupo ciano, grupo amino y grupo mono- o di-alquilamino.

Los ejemplos de anillo A incluyen un grupo pirimidinilo, un grupo piridilo, un grupo triazolilo, un grupo tetrazolilo, un grupo oxadiazolilo, un grupo dihidropirimidinilo, un grupo pirazinilo, un grupo tiazolilo, un grupo oxazolilo, un grupo dihidrooxazinilo, un grupo imidazolilo, un grupo pirazolilo, un grupo dihidropirazinilo, y lo similar.

Los compuestos más preferibles incluyen aquéllos en donde el anillo A es un grupo pirimidinilo, un grupo piridilo, un grupo tetrazolilo, un grupo oxadiazolilo, un grupo pirazinilo, un grupo tiazolilo o un grupo oxazolilo; y

R^{11} es un grupo carboxilo; un grupo ciano; un grupo nitro; un grupo alquilo sustituido por un grupo seleccionado de grupo hidroxilo, grupo ciano, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo, grupo hidroxialcoxilo, grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- ó di-alquilsulfamoilamino, grupo mono- ó di-alquilureido

opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo dialquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y grupo morfolinilo; un grupo alquenilo opcionalmente sustituido por grupo carboxilo; un grupo alcoxilo sustituido por un grupo seleccionado de grupo hidroxilo, grupo ciano, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo, grupo hidroxialcoxilo, grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- ó di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y grupo morfolinilo; un grupo alcoxicarbonilo; un grupo hidroxicarbamimidoilo; grupo alquiltio; un grupo alquilsulfonilo opcionalmente sustituido por grupo carboxilo; un grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxilo o grupo mono- o di-alquilamino; un grupo morfolinilo; un grupo tiomorfolinilo opcionalmente oxidado; un grupo piperazinilo

opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo; un grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilo; un grupo piperidinyl opcionalmente sustituido por el grupo carboxilo, grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilo; un grupo tetrazolilo opcionalmente sustituido por grupo alquilo, grupo hidroxialquilo, o grupo morfolinilalquilo; un grupo oxodihidrooxadiazolyl; un grupo pirimidinilo; o un grupo tetrahidropiranilo.

Los compuestos más preferidos aún incluyen aquéllos en donde R^1 es un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo y grupo alcoxicarbonilo), grupo alquenilo, átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo

hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); y grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); o un grupo dihidrooxazolilo opcionalmente sustituido por 1 o 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo;

R^{10} es un grupo fenilo sustituido por 1 a 3 sustituyentes seleccionados de grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, átomo halógeno y grupo ciano;

el anillo A es un grupo pirimidinilo, un grupo piridilo, un grupo tetrazolilo, un grupo oxadiazolyl o un grupo tiazolilo; y

R^{11} es un grupo carboxilo; un grupo ciano; un grupo nitro; un grupo alquilo sustituido por un grupo seleccionado

de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo, grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilammo, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y grupo morfolinilo; un grupo alquenilo opcionalmente sustituido por grupo carboxilo; un grupo alcoxilo sustituido por grupo seleccionado del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo, grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y grupo morfolinilo; un grupo hidroxicarbamimidoilo; un grupo alquiltio; un grupo alquilsulfonilo opcionalmente sustituido por grupo alcoxicarbonilo; un grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo o grupo alcoxilo; un grupo morfolinilo; grupo tiomorfolinilo opcionalmente oxidado; un grupo piperazinilo opcionalmente

sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo; un grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilo; un grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilo; un grupo tetrazolilo opcionalmente sustituido por grupo alquilo, grupo hidroxialquilo, o grupo morfolinilalquilo; un grupo oxodihidrooxadiazolilo; un grupo pirimidinilo; o un grupo tetrahidropiranilo.

Los compuestos aún más preferidos incluyen aquéllos en los cuales R^1 es un grupo alcoxicarbonilo opcionalmente sustituido por 1 o 5 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo hidroxilo y grupo cicloalquilo;

R^{10} es un grupo fenilo sustituido por 1 a 3 sustituyentes seleccionados del grupo ciano, grupo alquilo opcionalmente sustituido por átomo halógeno y grupo alcoxilo;

el anillo A es un grupo pirimidinilo, un grupo piridilo, un grupo tetrazolilo o un grupo oxadiazolilo;

R^{11} es un grupo carboxilo; un grupo alquilo sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxilo o grupo alquilsulfonilo; un grupo alquenilo opcionalmente sustituido por grupo carboxilo; un grupo alcoxilo sustituido por grupo ciano, grupo carboxilo, grupo hidroxilo, grupo alcoxilo,

grupo alquiltio o grupo alquilsulfonilo; un grupo mono- o di-alquilamino opcionalmente sustituido por grupo carboxilo o grupo alcoxilo; un grupo morfolinilo; un grupo piperidinilo sustituido por grupo carboxilo; o un grupo tetrazolilo sustituido por grupo hidroxiloalquilo;

R^7 es un grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, o grupo mono o di-alquilamino; y.

R^8 es un átomo de hidrógeno.

Los compuestos especialmente preferidos incluyen aquéllos en los cuales R^1 es un grupo etoxicarbonilo, un grupo hidroxietoxicarbonilo, un grupo 2-fluoroetoxicarbonilo, un grupo 2,2-difluoroetoxicarbonilo o un grupo 2,2,2-trifluoroetoxicarbonilo; R^2 es un grupo etilo; R^{10} es un grupo fenilo sustituido por 1 a 2 sustituyentes seleccionados del grupo ciano, grupo trifluorometilo y grupo metoxilo; R^7 es un grupo trifluorometilo o un grupo metoxilo, otros ejemplos de compuestos especialmente preferidos incluyen aquéllos en donde R^1 es un grupo carboxi(alcoxi C_{2-10})carbonilo o un grupo alcoxicarbonil(alcoxi C_{2-10})carbonilo R^2, R^{10} y R^7 son iguales a los definidos precedentemente.

Los compuestos especialmente más preferidos incluyen aquéllos en donde R^1 es un grupo etoxicarbonilo o un grupo hidroxietoxicarbonilo; R^2 es un grupo etilo; R^{10} es un grupo fenilo sustituido por 1 a 2 sustituyentes seleccionados del grupo ciano, grupo trifluorometilo y grupo metoxilo; R^7 es un

grupo trifluorometilo o un grupo metoxilo.

Los compuestos más preferibles incluyan los enumerados a continuación.

Etil éster de ácido (2R,4S)-4-([3,S-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il])amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[[3,5-Bis(trifluorometil)bencil]-(5-{[metil-(2-metoxietil)]-amino]pirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil}-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2etil-6-trifluorometil-3,4-dihidro-2H-quinolir-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-(5-carboxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-carboxietil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-(5-[2-(2-hidroxietil)-2H-tetrazol-5-il]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-

dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3,5-Dimetoxibencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3,5-Dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3-Cianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-{5-[2-(2-hidroxietil)-2H-tetrazol-5-il]pirimidin-2-il}}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2-hidroxietil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil][2-(2-metansulfoniletil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-

quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Hidroxiletil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-{5-(2-carboxietil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-[[3,5-Bis(trifluorometil)bencil]-(5-{[metil-(2-carboxietil)]amino)pirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-{5-[3-(tetrazol-5-il)propoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxibutoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-[5-(5-carboxipentiloxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-{5-(2-carboxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboximetilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-[5-(4-carboxibutoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-((3-Ciano-5-trifluorometilbencil)-[S-(4-carboxibutoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolina-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-dimetilamino-3,4-dihidro-2H-quinolin-1-carboxílico;

2,2,2-Trifluoroetil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2,2,2-Trifluoroetil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-

il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2,2,2-Trifluoroetil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(3-carboxipropoxi)-pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Hidroxiletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico; ó

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico; ó

una sal farmacéuticamente aceptable del mismo.

Los ejemplos adicionales mas preferibles de los compuestos incluyen:

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-

il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-

il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6,7-etilendioxi-3,4-dihidro-2H-quinolin-1-carboxílico; ó

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6,7-etilendioxi-3,4-dihidro-2H-quinolin-1-

carboxílico;

o una sal farmacéuticamente aceptable del mismo.

El presente compuesto (I) o una sal farmacéuticamente aceptable del mismo puede ser administrada oralmente o parenteralmente, y puede ser formulada en preparaciones farmacéuticas con vehículos farmacéuticamente aceptables utilizados convencionalmente.

Las sales farmacéuticamente aceptables del compuesto (1) pueden incluir, por ejemplo, sal de metal alcalino tal como sal de litio, sodio o potasio; las sales de metal alcalino térreo tales como sal de calcio o magnesio; las sales con zinc o aluminio; las sales con bases orgánicas tales como amonio, colina, dietanolamina, lisina, etilendiamina, terc-butilamina, terc-octilamina, tris(hidroximetil)aminometano, N-metilglucosamina, trietanolamina o deshidroabietilamina; las sales con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido hidroiódico, ácido sulfúrico, ácido nítrico o ácido fosfórico; las sales con ácidos orgánicos tales como ácido fórmico, ácido acético, ácido propiónico, ácido oxálico, ácido malónico, ácido succínico, ácido fumárico, ácido maléico, ácido láctico, ácido málico, ácido tartárico, ácido cítrico, ácido metansulfónico, ácido etansulfónico, ácido bencensulfónico o ácido toluensulfónico; o las sales derivadas desde aminoácidos ácidos tales como ácido aspártico o ácido glutámico.

Adicionalmente, las sales farmacéuticamente aceptables del compuesto (I) pueden incluir, por ejemplo, las sales cuaternarias formadas entre un compuesto de la fórmula (I) y un haluro de alquilo o haluro de fenilalquilo.

Las preparaciones farmacéuticas preferidas para la administración oral del presente compuesto (I) o una sal farmacéuticamente aceptable del mismo incluyen las formulaciones sólidas tales como las tabletas, gránulos, cápsulas o polvos; y formulaciones líquidas tales como las soluciones, suspensiones o emulsiones. Las preparaciones farmacéuticas preferidas para la administración parenteral incluyen inyecciones o infusiones formuladas con agua destilada inyectable, solución salina fisiológica o solución de glucosa acuosa; supositorios; o preparación de inhalación.

Estas preparaciones farmacéuticas comprender un compuesto (I) de la presente invención o una sal farmacéuticamente aceptable del mismo y un portador farmacéuticamente aceptable que normalmente es utilizado para la administración oral o parental. Los portadores farmacéuticamente aceptables para la administración oral incluyen, por ejemplo, un aglomerante (jarabe, goma de acacia, gelatina, sorbitán, tragacanto, polivinilpirrolidona, y lo similar), un vehículo (lactosa, azúcar, almidón de maiz, fosfato de potasio, sorbitán, glicina, y lo similar), un lubricante (estearato de magnesio, talco, polietilén glicol,

sílice, y lo similar), una desintegrante (fécula de papa, y lo similar), y un agente humectante (sulfato de lauril sodio anhidro, y lo similar). Los portadores farmacéuticamente aceptables para la administración parenteral incluyen, por ejemplo, agua destilada inyectable, solución salina fisiológica y solución de glucosa acuosa.

La dosis de un compuesto (I) de la presente invención o una sal farmacéuticamente aceptable del mismo varía, dependiendo de la vía de administración, edad, peso del cuerpo, enfermedad, y condición/severidad, del paciente. Sin embargo normalmente puede estar dentro del rango de aproximadamente 0,001 - 1,000 mg/kg/día, más preferentemente dentro del rango de aproximadamente 0,01 - 100 mg/kg/día.

Los compuestos de la presente invención tienen una actividad inhibitoria contra CETP y demuestra efectos de incremento del colesterol HDL y disminución del colesterol LDL. Consiguientemente, los mismos son útiles en la profilaxis o tratamiento de un sujeto (particularmente, mamífero inclusive el ser humano) que padece arterioesclerosis, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia de origen familiar, enfermedades cardiovasculares, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio,

lesión de reperfusion, restenosis después de angioplastia, hipertensión, infarto cerebral, accidente cerebral, diabetes, complicación vascular de diabetes, enfermedades trombóticas, obesidad, endotoxemia, o lo similar.

Adicionalmente, pueden usarse los compuestos de la presente invención en combinación con otras drogas útiles para tratamiento de estas enfermedades. Por ejemplo, puede usarse un compuestos de la presente invención en combinación con un inhibidor de síntesis de colesterol tal como el inhibidor de HMG-CoA reductasa, un inhibidor de absorción de colesterol tal como resina de intercambio de anión, fibratos, un agente para disminución de triglicérido tal como niacina u otro reductor de colesterol tal como el inhibidor de ACAT.

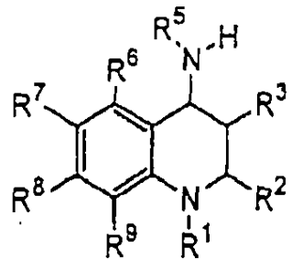
Los compuestos de la presente invención se caracterizan por que un grupo amino sustituido por un heterociclo que tiene un sustituyente(s) según lo definido anteriormente es introducido en la posición 4 del esqueleto de tetrahidroquinolina, por lo cual los mismos pueden exhibir una actividad inhibitoria excelente contra CETP y pueden tener una biodisponibilidad mejorada. Ante todo, los compuestos que tienen un grupo carboxilo en la posición terminal de sustituyentes resepctivos R^1 - R^{11}, especialmente se prefieren aquéllos que tienen un grupo carboxilo en la posición terminal R^1 y/o R^5, ó R^1 y/o R^{11}.

El compuesto (I) de la presente invención puede ser

preparado por los métodos siguientes.

PROCEDIMIENTO 1

El compuesto (I) de la presente invención puede ser preparado por condensación de un compuesto de la fórmula (II):



(II)

en donde los símbolos tienen el mismo significado como el definido anteriormente con un compuesto de la fórmula (III):

R^{10}-R^4-Z^1 (III)

en donde Z^1 es un grupo de partida y los otros símbolos tienen el mismo significando como el definido anteriormente.

La condensación puede ser llevada a cabo en presencia de una base en un solvente conveniente.

El grupo de partida incluye un átomo halógeno inclusive átomo de cloro, átomo de bromo, átomo de iodo, y un grupo sulfoniloxilo sustituido agrupan incluyendo grupo metansulfoniloxilo, grupo p-toluensulfoniloxilo, grupo trifluorometansulfoniloxilo.

Una base convencional puede ser utilizada como base, y por ejemplo, hidruro de metal alcalino que incluye el hidruro de sodio, hidruro de potasio; hidróxido de metal alcalino que incluye hidróxido de sodio, hidróxido de potasio; hicróxido

de metal alcalino-térreo que incluye hidróxido de bario; alcóxido de metal alcalino que incluye metóxido de sodio, etóxido de sodio, etóxido de potasio, terc-butóxido de potasio; carbonato de metal alcalino que incluye carbonato de sodio, carbonato de potasio, carbonato de cesio; bicarbonato de metal alcalino que incluye bicarbonato de sodio, bicarbonato de potasio; amina que incluye trietilamina, diisopropiletilamina, metilpiperidine, xilidina, 1,8-diazabiciclo[5.4.0]undeceno, 1,4-diazabiciclo[2.2.2]octano, 1,5-diazabiciclo[4.3.0]noneno; piridinas que incluyen piridina, preferentemente puede usarse dimetilaminopiridina.

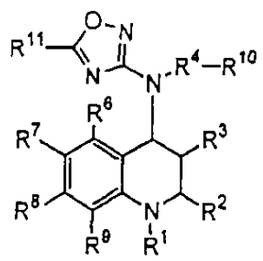
Cualquier solvente cuya dosis no perturbe la reacción puede ser usado preferentemente, y tal solvente incluye, por ejemplo, hidrocarburos que incluyen pentano, hexano; hidrocarburos aromáticos que incluyen benceno, tolueno, nitrobenceno; hidrocarburos halogenados que incluyen diclorometano, cloroformo; éteres que incluyen dietiléter, tetrahidrofurano; amidas que incluye dimetilformamida, N-metilpirrolidona, 1,3-dimetilimidazolidin-2-ona; sulfóxidos que incluyen dimetilsulfóxido; alcoholes que incluyen metanol, etanol; ésteres que incluyen acetato de etilo, acetato de butilo; cetonas que incluyen acetona, etilo metil cetona; nitrilos que incluyen acetonitrilo; agua, o un solvente mezcla de los mismos.

La reacción puede ser realizada bajo enfriamiento como

bajo calentamiento, preferentemente desde -78°C a 200°C, más preferentemente desde -30°C hasta 100°C.

PROCEDIMIENTO 2

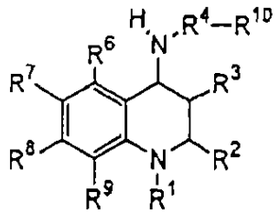
Entre el compuesto de la fórmula (I-A), un compuesto de la fórmula (I-b):



(I-b)

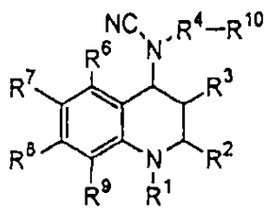
en donde los símbolos tienen el mismo significado como definido anteriormente puede ser preparado por

(a) cianación de un compuesto de la fórmula (IV):



(IV)

en donde los símbolos tienen el mismo significado como el definido anteriormente para proveer un compuesto de la fórmula (V):

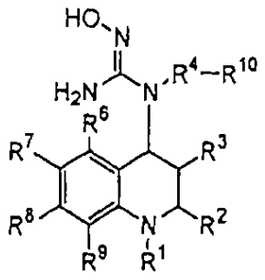


(V)

en donde los símbolos tienen el mismo significado como el

definido anteriormente,

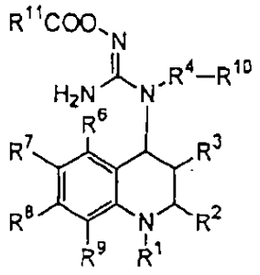
(b) hacer reaccionar el compuesto (V) con hidroxilamina o una sal del mismo para proveer un compuesto de la fórmula (VI):



(VI)

en donde los símbolos tienen el mismo significado como el definido anteriormente,

(c) alcanoilación del compuesto (VI) para proveer un compuesto de la fórmula (VII):



(VII)

en donde los símbolos tienen el mismo significado como el definido anteriormente, y además

(d) ciclizar el compuesto (VII) con una base.

La cianación en el procedimiento (a) puede ser realizada haciendo reaccionar un cianógeno halogenado en presencia de una base en un solvente conveniente.

El bromuro de cianógeno es preferible como cianógeno halogenado.

Una base convencional puede ser usada preferentemente como base, y preferentemente puede ser usado carbonato de metal alcalino que incluye carbonato de potasio, o bicarbonato de metal alcalino que incluye bicarbonato de sodio.

Puede ser usado cualquier solvente cuya dosificación no perturbe la reacción y preferentemente puede ser utilizado el solvente indicado en el PROCEDIMIENTO 1.

La reacción con hidroxilamina en el procedimiento (b) puede ser realizada en presencia de una base en un solvente conveniente.

Las alquilaminas terciarias que incluyen trietilamina, diisopropiletilamina, y lo similar pueden ser usadas preferentemente como base.

Puede ser usado cualquier solvente cuya dosificación no perturbe la reacción y preferentemente puede ser utilizado el solvente indicado en el PROCEDIMIENTO 1.

La alcanoilación en el procedimiento (c) puede ser realizada con un haluro de alcanoilo en presencia de una base en un solvente conveniente.

Una base convencional puede ser usada como la base, y amina que incluye trietilamina o diisopropiletilamina, o piridina que incluye piridina, pueden usarse preferentemente 4-dimetilaminopiridina.

Puede ser usado cualquier solvente cuya dosificación no

perturbe la reacción y preferentemente puede ser utilizado el solvente indicado en el PROCEDIMIENTO 1.

En la ciclisación en el procedimiento (d), una base convencional puede ser usada como base, y amina que incluye trietilamina o diisopropiletilamina; preferentemente pueden usarse piridina que incluye piridina, 4-dimetilaminopiridina; o alcóxido de metal alcalino incluyendo metóxido de sodio.

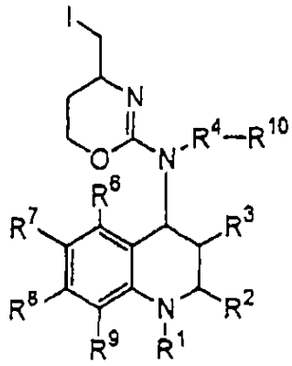
Puede ser usado cualquier solvente cuya dosificación no perturbe la reacción y preferentemente puede ser utilizado el solvente indicado en el PROCEDIMIENTO 1.

Adicionalmente, la ciclización siguiente a la alcanoilación también puede ser realizada in situ.

La reacción puede ser realizada bajo enfriamiento como bajo calentamiento, preferentemente desde -50°C hasta 100°C, más preferentemente desde 0°C hasta 50°C.

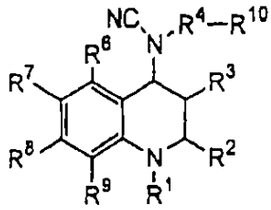
PROCEDIMIENTO 3

Entre el compuesto de la fórmula (I-A), un compuesto de la fórmula (I-c):



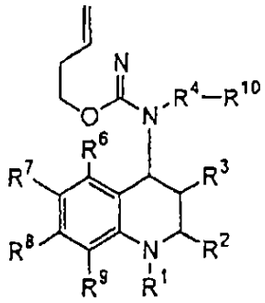
(I-c)

en donde los símbolos tienen el mismo significado como el definido anteriormente puede ser preparado haciendo reaccionar un compuesto de la fórmula (V):



(V)

en donde los símbolos tienen el mismo significado como el definido anteriormente con 3-buten-1-ol para proveer un compuesto de la fórmula (VIII):



(VIII)

en donde los símbolos tienen el mismo significado como el definido anteriormente, seguido por la ciclización del compuesto resultante en presencia de iodo, N-iodosuccinimida, o lo similar.

La reacción con 3-buten-1-ol puede ser realizada en presencia de una base en un solvente conveniente.

Cualquier base que dosifica no perturbe la reacción puede ser usada y puede usarse preferentemente la base indicada en el PROCEDIMIENTO 1.

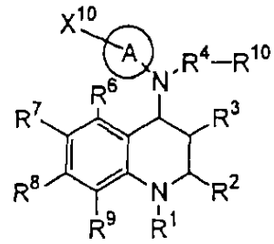
Puede ser usado cualquier solvente cuya dosificación no perturbe la reacción y preferentemente puede ser utilizado el solvente indicado en el PROCEDIMIENTO 1.

En la ciclización cualquier solvente cuya dosificación no perturbe la reacción puede ser usado y puede usarse preferentemente el solvente indicado en el PROCEDIMIENTO 1.

La reacción puede ser realizada bajo enfriamiento como bajo calentamiento, preferentemente desde -50°C hasta 100°C, más preferentemente desde 0°C hasta 50°C.

PROCEDIMIENTO 4

El compuesto de la fórmula (I-A) también puede ser preparado por medio de los métodos siguientes con un compuesto de la fórmula (IX):



(IX)

en donde X^{10} es un átomo de hidrógeno, un átomo halógeno o un grupo hidroxilo y los otros símbolos tienen el mismo significado como el definido anteriormente.

En cada procedimiento de los siguientes (A) a (K), a menos que sea especificado de otra manera, la base indicada en el PROCEDIMIENTO 1 puede ser usada preferentemente como la base.

Adicionalmente, en cada procedimiento siguiente (A) a (K) un ácido convencional puede ser usado como un ácido, y a menos que sea especificado de otra manera, puede usarse preferentemente un ácido mineral que incluye el ácido clorhídrico, ácido nítrico, el ácido sulfúrico; un ácido orgánico representado por ácido sulfónico (por ejemplo, ácido metansulfónico, ácido p-toluensulfónico, ácido trifluorometansulfónico, y lo similar).

Adicionalmente, en cada procedimiento siguiente (A) a (K), puede usarse como solvente cualquier solvente cuya dosificación no perturbe la reacción, y específicamente, puede usarse preferentemente el solvente indicado en el PROCEDIMIENTO 1.

El grupo de partida incluye un átomo halógeno que incluye átomo de cloro, átomo de bromo, átomo de iodo, y un grupo sulfoniloxilo sustituido que incluye grupo metansulfoniloxilo, y grupo trifluorometansulfonilcxilo, grupo toluensulfoniloxilo.

(A) El compuesto en donde el anillo A es un grupo tetrazolilo y R^{11} es un grupo alquilo que posee 3 a 10 átomos de carbono o un grupo alquilo sustituido puede ser preparado por

alquilación de un compuesto de la fórmula (IX) en donde el anillo A es un grupo tetrazolilo y X^{10} es un átomo de hidrógeno.

La alquilación puede ser realizada haciendo reaccionar un compuesto comienzo con un compuesto de la fórmula:

$$R^{11A}-Z^2$$

en donde R^{11A} es un grupo alquilo que posee 3 a 10 átomos de carbono o un grupo alquilo sustituido y Z^2 se refiere a un grupo de partida en un solvente conveniente en presencia o ausencia de una base, o haciendo reaccionar un compuesto de la fórmula:

$$R^{11A}-OH$$

en donde el simbolo posee el mismo significado como el definido anteriormente en un solvente conveniente en presencia de fosfinos y ésteres azodicarboxílicos.

La reacción procede más preferentemente cuando se agrega una cantidad catalítica de un yoduro de metal alcalino (por ejemplo, yoduro de potasio, y lo similar).

Preferentemente pueden ser utiliza ambos fosfinos y ésteres azodicarboxílicos que normalmente se utilizan en la reacción de Mitsunobu. Por ejemplo, los fosfinos incluyen trifenilfosfino, tributilfosfino, y lo similar, y los ésteres azodicarboxílicos incluyen dietil azodicarboxilato, diisopropil azodiformato, y lo similar.

(B) El compuesto en donde el anillo A es grupo 2-

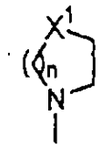
oxodihidropirimidinilo y R^{11} es un grupo alquilo que posee 3 a 10 átomos de carbono o un grupo alquilo sustituido puede ser preparado por alquilación de un compuesto de la fórmula (IX) en donde el anillo A es grupo 2-hidroxipirimidinilo y X^{10} es un átomo de hidrógeno con un compuesto de la fórmula:

$$R^{11A}-Z^2$$

en donde los símbolos tienen el mismo significado como el definido anteriormente.

La reacción puede ser realizada de la misma manera como en (A).

(C) El compuesto en donde R^{11} es un grupo amino opcionalmente sustituido o un grupo de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente puede ser preparado haciendo reaccionar un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno con un amina correspondiente o un compuesto de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente.

La reacción puede ser realizada en presencia o ausencia de una base, y en presencia o ausencia de un catalizador de paladio en un solvente conveniente.

Como catalizador de paladio, puede usarse un catalizador de paladio convencional el acetato del paladio incluyendo, tetrakis(trifenilfosfina)paladio, tris(dibencilidenacetona)dipaladio, diclorobis(trifenilfosfina)-paladio, diclorobis(tri-o-tolilfosfina)paladio, acetato de bis-(trifenilfosfina)paladio, o lo similar.

Como la base, puede usarse hidróxido metal alcalino incluso hidróxido de sodio, hidróxido de potasio; hidróxido de metal alcalino térreo incluso hidróxido de bario; alcóxido de metal alcalino incluso metóxido de sodio, etóxido de sodio, etóxido de potasio, terc-butóxido de potasio; carbonato de metal alcalino incluso carbonato de sodio, carbonato de potasio, carbonato de cesio; bicarbonato de metal alcalino incluso bicarbonato de sodio, bicarbonato de potasio; fosfato de metal alcalino incluso fosfato de potasio; amina incluso trietilamina, diisopropiletilamina, metilpiperidina, diciclohexilmetilamina; y piridinas incluso piridina, preferentemente 4-dimetilaminopiridine.

Adicionalmente, pueden agregarse fosfinas en la presente reacción. Como fosfinas, puede usarse preferentemente trifenilfosfina, tributilfosfina, tetrafluoroborato de tri-

terc-butilfosfonio, 1,3-bis(difenilfosfino)propano, 2,2'-bis(difenilfosfino)-1,1'-binaftilo, 1,1'-bis(difenilfosfino)ferroceno, 2-(di-terc-butilfosfino)bifenilo, 2-diciclohexilfosfino-2'-(N,N-dimetilamino)bifenilo, 2-(diciclohexilfosfino)bifenilo, y lo similar como fosfinas.

(D) El compuesto en donde R^{11} es un grupo amino opcionalmente sustituido puede ser preparado acoplando un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno con un compuesto de la fórmula:

$$(R^{20})_3Sn\text{-}NR^{21}R^{22}$$

en donde R^{20} es un grupo alquilo y $NR^{21}R^{22}$ es un grupo amino opcionalmente sustituido.

La reacción de acoplamiento puede ser realizada en presencia de un catalizador de paladio en presencia o ausencia de una base en un solvente conveniente.

Los catalizadores de paladio, bases, y fosfinas indicadas en (C) pueden usarse de la misma manera como (C) anteriormente.

(E) El compuesto en donde R^{11} es un grupo ciano puede ser preparado por la cianación de un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno.

La cianación pueden ser realizada haciendo reaccionar un compuesto de comienzo con un cianuro de metal que incluye el cianuro de sodio, cianuro de potasio, o cianuro de zinc en

presencia de un catalizador de paladio en un solvente conveniente.

El mismo catalizador de paladio como el descripto en (C) puede usarse preferentemente.

(F) El compuesto en donde R^{11} es un grupo alcoxicarbonilo opcionalmente sustituido puede ser preparado haciendo reaccionar un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno con un alquilalcohol correspondiente bajo monóxido de carbono usando un catalizador de paladio en presencia de una base en un solvente conveniente.

El mismo catalizador de paladio y base como los descriptos en (C) pueden usarse preferentemente.

Adicionalmente, la reacción puede ser realizada más preferentemente agregando un ligando, y las fosfinas indicadas en (C) pueden usarse preferentemente como ligando.

(G) El compuesto en donde R^{11} es un grupo alquenilo opcionalmente sustituido puede ser preparado acoplando un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno con un alqueno correspondiente.

La reacción de acoplamiento puede ser realizada en presencia de un catalizador de paladio en presencia o ausencia de una base en un solvente conveniente.

El mismo catalizador de paladio como el descripto en (C) puede usarse preferentemente.

La misma base como la indicada en (C) puede ser usada

preferentemente y también puede usarse carbonato de plata.

Adicionalmente, la reacción puede ser realizada más preferentemente agregando un ligando, y las fosfinas indicadas en (C) pueden usarse preferentemente como ligando.

(H) El compuesto en donde R^{11} es un grupo alcoxilo que posee 3 a 10 átomos de carbono o un grupo alcoxilo sustituido que puede ser realizado por alcoxilación de un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno.

La alcoxilación pueden ser realizada agregando opcionalmente un catalizador de cobre para hacer reaccionar un compuesto de comienzo con un alcohol correspondiente en un solvente conveniente o diluyente en presencia de una base.

La misma base como se indica en (C), en particular, puede usarse preferentemente el carbonato de cesio.

El catalizador de cobre que incluye el yoduro de cobre, bromuro de cobre, cloruro de cobre, acetato de cobre, trifluorometansulfonato de cobre, y lo similar puede usarse preferentemente.

Adicionalmente, la reacción procede más preferentemente cuando se agrega 1,10-fenantrolina, 2-aminopiridina, o lo similar.

(I) El compuesto en donde R^{11} es un grupo heterocíclico opcionalmente sustituido que puede ser preparado acoplando un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno con un ácido borónico de heterocíclico correspondiente o un

éster borónico de heterocíclico correspondiente.

El acoplamiento puede ser realizado en presencia un catalizador de paladio, y en la presencia o ausencia de una base en un solvente conveniente.

La reacción puede ser realizada de la misma manera como (C).

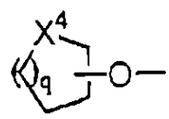
(J) El compuesto en donde R^{11} es un grupo alcoxicarbonilalquilsulfonilo puede ser preparado haciendo reaccionar un compuesto de la fórmula (IX) en donde X^{10} es un átomo halógeno con una sal de metal alcalino de ácido alcoxicarbonilalquilsulfínico.

La sal de metal alcalino de ácido alcoxicarbonilalquilsulfínico puede ser preparada según el método descripto, por ejemplo, en Baskin y col., "Tetrahedron Lett.", 43, 8479 (2002).

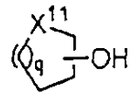
Adicionalmente, la reacción puede ser realizada en presencia de un catalizador de cobre en un solvente conveniente según el método descrito en la literatura.

El mismo catalizador de cobre como el descripto en (H) puede ser utilizado, y en particular, puede usarse preferentemente el yoduro de cobre.

(K) El compuesto en donde R^{11} es un grupo de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente puede ser preparado condensando un compuesto en donde R^{11} es un grupo hidroxilo con un compuesto de la fórmula:



en donde X^{11} es O, SO, SO_2 o NR^P (R^P es un grupo protector) y q es un entero de valor 1 a 4, y si es necesario, eliminar un grupo protector para el grupo amino.

Como un grupo protector para el grupo amino, puede usarse un grupo protector convencional que incluye grupo benciloxicarbonilo, grupo terc-butoxicarbonilo, y lo similar.

La reacción puede ser realizada en un solvente conveniente en presencia de fosfinas y ésteres azodicarboxílicos. La reacción puede ser realizada de la misma manera como el PROCEDIMIENTO 4-(A).

La eliminación de un grupo protector puede ser realizada de una manera convencional que incluye la reducción catalizadora, tratamiento ácido, y lo similar, dependiendo del tipo de grupo protector.

Las reacciones (A) a (K) para las conversiones de R^{11} también pueden ser aplicadas para la conversión de igual manera para otro sustituyente (R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 ó R^{10}) según sea apropiado.

Adicionalmente, un sustituyente(s) de un compuesto (I)

de la presente invención puede convertirse en diferente(s) dentro del alcance del compuesto (I) según los métodos siguientes según sea lo apropiado.

En la continuación de cada procedimiento, una base convencional puede ser usada como base, y a menos que sea especificado de otra manera, puede usarse preferentemente la base es la indicada en el PROCEDIMIENTO 1.

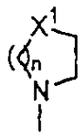
Adicionalmente, siguiendo cada procedimiento, un ácido convencional puede ser usado como ácido, y a menos que sea especificado de otra manera, puede usarse preferentemente un ácido mineral que incluye ácido clorhídrico, ácido nítrico, ácido sulfúrico, o un ácido orgánico representado por ácido sulfónico (por ejemplo, ácido metansulfónico, ácido p-toluensulfónico, ácido trifluorometansulfónico) o ácidos carboxílicos (por ejemplo, ácido acético, ácido trifluoracético).

Además adicionalmente, siguiendo cada procedimiento, puede usarse cualquier solvente cuya dosificación no perturbe la reacción, y como tal, puede usarse preferentemente el solvente indicado en el PROCEDIMIENTO 1.

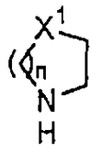
El grupo de partida incluye un átomo halógeno que incluye átomo de cloro, átomo de bromo, átomo de yodo, y un grupo sulfoniloxilo sustituido que incluye grupo metansulfoniloxilo, grupo trifluorometansulfoniloxilo, y grupo toluensulfoniloxilo.

Adicionalmente a lo anterior, siguiendo cada procedimiento, "un grupo monocíclico saturado o no saturado o grupo heterocíclico bicíclico que posee independientemente uno a cuatro heteroátomos seleccionados del átomo de oxigeno, átomo de azufre y átomo de nitrógeno" en R^5 es simplemente denominado "un grupo heterocíclico".

(1) El compuesto en donde R^5 es un grupo heterocíclico sustituido por un grupo amino opcionalmente sustituido o un grupo de la fórmula:



en donde los símbolos poseen el mismo significado como el definido anteriormente puede ser preparado haciendo reaccionar un compuesto (I) en donde R^5 es un grupo heterocíclico sustituido por un grupo alquilsulfoniloxilo opcionalmente sustituidos con una amina correspondiente o un compuesto de la fórmula:

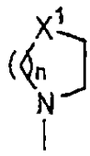


en donde los símbolos tienen el mismo significado como el definido anteriormente en presencia de un catalizador de paladio, y en presencia o ausencia de una base en un solvente o diluyente conveniente.

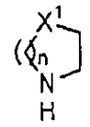
La reacción puede ser realizada de la misma manera como

en el PROCEDIMIENTO 4-(C).

(2) el compuesto en donde R^5 es un grupo heterocíclico sustituido por un grupo amino opcionalmente sustituido o un grupo de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente también puede ser preparado haciendo reaccionar un compuesto en donde R^5 es un grupo heterocíclico sustituido por un átomo halógeno o un grupo alquilsulfoniloxilo opcionalmente sustituido con una amina correspondiente o un compuesto de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente.

La reacción puede ser realizada agregando opcionalmente un catalizador de cobre en presencia o ausencia de una base en un solvente conveniente.

El yoduro de cobre, bromuro de cobre, cloruro de cobre, acetato de cobre, trifluorometansulfonato de cobre, y lo similar puede usarse preferentemente como catalizador de cobre.

La misma base como la indicada en el PROCEDIMIENTO 4-(C) puede ser usada preferentemente.

Adicionalmente, la reacción procede más preferentemente cuando es agregado N,N'-dimetiletilendiamina, 1,10-fenantrolina, etilén glicol, fenilfenol, y lo similar.

(3) El compuesto en donde R^5 es un grupo heterocíclico sustituido por un grupo alquiltio opcionalmente sustituido puede ser preparado haciendo reaccionar un compuesto en donde R^5 es un grupo heterocíclico sustituido por un átomo halógeno o un grupo alquilsulfoniloxilo opcionalmente sustituido con un alquiltio correspondiente.

La reacción puede realizarse previamente de la misma manera como fue descripto en el PROCEDIMIENTO 4-(H) y es facilitada agregando 1,10-fenantrolina o etilén glicol.

(4) El compuesto en donde R^5 es un grupo heterocíclico sustituido por un grupo heterocíclico opcionalmente sustituido puede ser preparado acoplando un compuesto en donde R^5 es un grupo heterocíclico sustituido por un átomo halógeno o un grupo alquilsulfoniloxilo opcionalmente sustituido con un heterocíclico alquilo estaño compuesto correspondiente.

La reacción puede ser realizada de la misma manera como en el PROCEDIMIENTO 4-(D).

(5) El compuesto en donde R^5 es un grupo heterocíclico sustituido por un grupo alcoxilo o un grupo

alcoxifenilalcoxilo puede ser preparado haciendo reaccionar un compuesto en donde R^5 es un grupo heterocíclico sustituido por un grupo alquilsulfonilo con un alcóxido de metal alcalino correspondientes en un solvente conveniente. Los alcóxidos de metal alcalin correspondientes pueden ser obtenidos tratando un alquilalcohol correspondiente con hidruro de metal alcalino o metal alcalino en dicho solvente.

(6) El compuesto que posee un grupo aminoalquilo como sustituyente en R^5 puede ser preparado reduciendo catalíticamente un compuesto que posee un grupo ciano o un grupo cianoalquilo como sustituyente en R^5.

La reducción catalizadora puede ser realizada usando un catalizador bajo hidrógeno en un solvente conveniente según una modalidad convencional. El catalizador incluye un catalizador de paladio que incluye paladio-carbono, un catalizador de níquel que incluye niquel Raney, un catalizador de platino que incluye platino carbono, y lo similar.

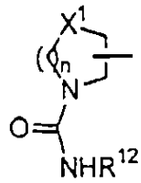
(7) El compuesto que posee un grupo mono- o di-alquilsulfamoilaminoalquilo opcionalmente sustituido como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo aminoalquilo como un sustituyente en R^5 con un mono- o di-alquilsulfamoilo halogenado correspondiente.

La reacción puede ser realizada en un solvente

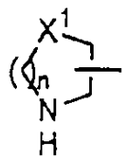
conveniente en presencia de una base.

(8) El compuesto que posee un grupo mono-alquilcarbamoilaminoalquilo opcionalmente sustituido como un sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo aminoalquilo como un sustituyente en R^5 con un isocianato de alquilo correspondiente en un solvente conveniente.

(9) El compuesto que posee un grupo de la fórmula:



en donde R^{12} es un grupo alquilo y el otro símbolo tiene el mismo significado como el definido anteriormente como un sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente como un sustituyente en R^5 con un isocianato de alquilo correspondiente ($R^{12}NCO$). La reacción puede ser realizada de la misma manera como en (8).

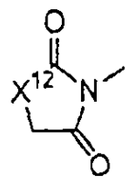
(10) El compuesto que posee un grupo mono- o di-

alquilcarbamoilaminoalquilo opcionalmente sustituido como un sustituyente en R^5 puede ser preparado condensando un compuesto que posee un grupo aminoalquilo como sustituyente en R^5 con un grupo mono- o di-alquilamina opcionalmente sustituido usando un agente de carbonilación en un solvente conveniente en presencia o ausencia de una base.

Puede usarse un agente de carbonilación convencional tal como carbonildiimidazol, fosgeno, trifosgeno, y lo similar.

(11) El compuesto que posee un grupo morfolinilcarbonilamino como sustituyente en R^5 puede ser preparado condensando un compuesto que posee un grupo amino como sustituyente en R^5 con tetrahidrooxazina usando un agente de carbonilación en un solvente conveniente. La reacción puede ser realizada de la misma manera como en (10).

(12) El compuesto que posee un grupo de la fórmula:



en donde X^{12} es O ó NH como sustituyente en R^5 puede ser preparado tratando un compuesto que posee un grupo de la fórmula

$$H\text{-}X^{12}\text{-}CH_2\text{-}CONH\text{-}$$

en donde los símbolos tienen el mismo significado como el definido anteriormente como sustituyente en R^5 con un agente

de carbonilación en un solvente conveniente.

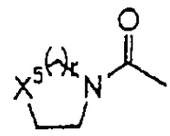
La reacción puede ser realizada de la misma manera como en (10).

(13) El compuesto que posee un grupo carbamoilo opcionalmente sustituido como sustituyente en R^5 puede ser preparado condensando un compuesto que posee un grupo carboxilo como sustituyente en R^5 con un amina conveniente.

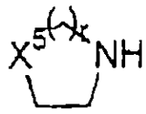
La condensación puede ser realizada usando un agente de condensación en un solvente conveniente. Puede usarse preferentemente un agente de condensación convencional tal como diciclohexilcarbodiimida, 1-etil-3-(3-dimetilaminopropil)carbodiimida, carbonildiimidazol, y lo similar.

Adicionalmente, la condensación puede ser realizada más preferentemente agregando un agente de activación que incluye 1-hidroxibenzotriazol, 1-hidroxisuccinimida, y lo similar.

(14) El compuesto que posee un grupo de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente como sustituyente en R^5 puede ser preparado condensando un compuesto que posee un grupo carboxilo como sustituyente en R^5 con un compuesto de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente.

La reacción puede ser realizada de la misma manera como en (13).

(15) El compuesto que posee un grupo tetrazolilo como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo ciano como sustituyente en R^5 con una azida de metal alcalino en presencia de un ácido en un solvente conveniente.

La azida de metal alcalino incluye azida de sodio, azida de litio, y lo similar.

Puede usarse preferentemente una sal de amonio de un hidrógeno halogenados que incluye cloruro de amonio como ácido.

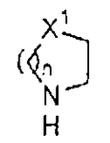
(16) El compuesto que posee un grupo tetrazolil alquilo opcionalmente sustituido como sustituyente en R^5 puede ser preparado por alquilación de un compuesto que posee un grupo tetrazolilo como sustituyente en R^5.

La alquilación puede ser realizada de la misma manera como en el PROCEDIMIENTO 4-(A).

(17) El compuesto que posee un grupo amino opcionalmente sustituido o un grupo de la fórmula:



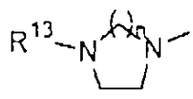
en donde los símbolos tienen el mismo significado como el definido anteriormente como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un átomo halógeno o un grupo alquilsulfoniloxilo opcionalmente sustituido como sustituyente en R^5 con una amina correspondiente o un compuesto de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente.

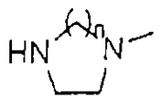
La reacción puede ser realizada preferentemente en presencia o ausencia de una base en un solvente conveniente.

(18) El compuesto que posee un grupo alquilamino opcionalmente sustituido o un grupo de la fórmula:



en donde R^{13} es un grupo alquilo opcionalmente sustituido por un grupo hidroxilo, un grupo alcoxicarbonilo, un grupo morfolinilo o un grupo fenilo, y n tiene el mismo significado como el definido anteriormente como sustituyente en R^5 puede

ser obtenido haciendo reaccionar un compuesto que posee un grupo amino o un grupo de la fórmula:

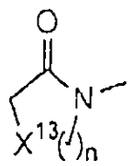


en donde los símbolos tienen el mismo significado como el definido anteriormente como sustituyente en R^5 con un haluro de alquilo correspondiente o un alquil éster sulfónico correspondiente.

El alquil éster sulfónico incluye éster metansulfónico, puede usarse preferentemente éster toluensulfónico, éster trifluorometansulfónico, y lo similar.

La reacción preferentemente puede ser realizada en presencia o ausencia de una base en un solvente conveniente.

(19) El compuesto que posee un grupo de la fórmula:



en donde X^{13} es O ó NH, y los otros símbolos tienen el mismo significado como el definido anteriormente como sustituyente en R^5 puede ser preparado cerrando el anillo de un compuesto que posee un grupo de la fórmula:

$$Z^3-(CH_2)_n-X^{13}-CH_2-CONH-$$

en donde Z^3 es un grupo de partida y los otros símbolos tienen el mismo significado como el definido anteriormente como

sustituyente en R^5.

La reacción puede ser realizada preferentemente en presencia o ausencia de una base en un solvente conveniente.

(20) El compuesto que posee un grupo carboxilo como sustituyente en R^5 puede ser preparado hidrolizando un compuesto que posee un grupo alcoxicarbonilo como sustituyente en R^5.

La hidrólisis puede ser realizada tratando un compuesto de comienzo con una base o un ácido en un solvente conveniente de acuerdo con una modalidad convencional. Un hidróxido de metal alcalino puede ser usado preferentemente como base.

(21) El compuesto que contiene un grupo carboxilo como sustituyente en R^5 puede ser preparado hidrolizando un compuesto que contiene un grupo ciano como sustituyente en R^5.

La hidrólisis puede ser realizada tratando un compuesto de comienzo con un ácido en un solvente conveniente.

(22) El compuesto que contiene un grupo carbamoilo como sustituyente en R^5 puede ser preparado hidrolizando un compuesto que contiene un grupo ciano como sustituyente en R^5.

La hidrólisis puede ser realizada tratando un compuesto de comienzo con un ácido en un solvente conveniente.

(23) El compuesto que posee un grupo carboxialquilo como sustituyente en R^5 también puede ser preparado reduciendo catalíticamente un compuesto que posee un grupo

carboxialquenilo, un grupo benciloxicarbonilalquenilo o un grupo benciloxicarbonilalquilo como sustituyente en R^5.

La reducción catalítica puede realizarse de la misma manera como en (6).

(24) El compuesto que posee un grupo hidroxilo como sustituyente en R^5 puede ser preparado hidrolizando un compuesto en donde R^5 posee un grupo alcanoiloxilo.

La hidrólisis puede ser realizada de la misma manera como en (20).

(25) El compuesto conteniendo sulfuro (SO) o sulfóxido (SO_2) en un sustituyente en R^5 puede ser preparado oxidando un compuesto que posee S en un sustituyente en R^5 (por ejemplo, un compuesto que posee un grupo tiomorfolinilo o un grupo alquiltioalquilo como sustituyente en R^5).

La oxidación puede ser realizada tratando un compuesto de comienzo con un agente oxidante en un solvente conveniente.

Los peróxidos tales como agua oxigenada, ácido m-cloroperbenzoico, hidroperóxido de acetilo, y lo similar pueden ser usados preferentemente como agente oxidante.

(26) El compuesto que contiene N-óxido en un sustituyente en R^5 puede ser preparado oxidando un compuesto que posee N en un sustituyente en R^5 (por ejemplo, un compuesto que posee un grupo piridilo como sustituyente en R^5).

La oxidación puede ser realizada de la misma manera como en (25).

(27) El compuesto que posee un grupo 1,2-dihidroxialquilo como sustituyente en R^5 puede ser preparado tratando un compuesto que posee un grupo alquilo sustituido por grupo mono- o di-alquildioxolanilo como sustituyente en R^5 con un ácido en un solvente conveniente.

Una resina fuertemente ácida también puede ser usada preferentemente como ácido, además de los descriptos previamente.

(28) El compuesto que posee un grupo alquilo sustituido por un grupo hidoxilo y un grupo alcoxilo opcionalmente sustituido como sustituyentes en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo oxilanilalquilo como sustituyente en R^5 con una sal de metal alcalino del alcohol correspondiente en un solvente conveniente.

La sal de metal alcalino de alcohol incluye una sal de litio, una sal de sodio, una sal de potasio, y lo similar.

(20) El compuesto que posee un grupo alquilo sustituido por un grupo hidoxilo y un grupo amino, o un grupo alquilo sustituido por un grupo hidroxilo y un grupo mono- o di-alquilamino opcionalmente sustituido como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo oxilanilalquilo como sustituyente en R^5 con amonio o un grupo mono- o di-alquilamino correspondiente en un solvente conveniente.

(30) El compuesto que posee un grupo hidroxicarbamimidoilo como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo ciano como sustituyente en R^5 con hidroxilamina o una sal del mismo en un solvente conveniente. Este procedimiento puede ser realizado de la misma manera como en el PROCEDIMIENTO 2-(b) descripto previamente.

(31) El compuesto que posee un grupo oxodihidroxadiazolilo como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo hidroxicarbamidoilo como sustituyente en R^5 con un agente de carbonilación en un solvente conveniente en presencia o ausencia de una base.

Puede usarse el mismo agente de carbonilación como el descripto en (10).

(32) El compuesto que posee un grupo sulfo como sustituyente en R^5 puede ser preparado por hidrolización de un compuesto que posee un grupo alcoxicarbonilalquilsulfonilo como sustituyente en R^5.

La hidrólisis puede ser realizada de la misma manera como en (20).

(33) El compuesto que posee un grupo sulfamoilo como sustituyente en R^5 puede ser preparado condensando un compuesto que posee un grupo sulfo como sustituyente en R^5 con un amina deseable.

La condensación puede ser realizada tratando un compuesto que posee un grupo sulfo como sustituyente en R^5 con un agente de halogenación en un solvente conveniente, seguido por hacer reaccionar el compuesto resultante con un amina conveniente en presencia o ausencia de una base.

El agente de halogenación convencional que puede usarse incluye haluro de tionilo, oxihaluro de fósforo, o lo similar. (34) El compuesto que posee un grupo hidroxiloalquilo como sustituyente en R^5 puede ser preparado por reducción de un compuesto que posee un grupo carboxialquilo como sustituyente en R^5, o convirtiendo el grupo carboxilo en un anhídrido ácido o un éster y reduciendo el compuesto resultante.

Un procedimiento para la conversión en un anhídrido de ácido puede ser realizado haciendo reaccionar un compuesto de comienzo con un formiato de alquilo halogenado en un solvente conveniente en presencia de una base.

Un procedimiento para la conversión en un éster puede ser realizado haciendo reaccionar compuesto de comienzo con un alcohol en presencia de un agente de condensación en un solvente conveniente. Este procedimiento puede ser realizado de la misma manera como en (33) solamente que un alcohol deseable es usado en lugar de la amina.

La reducción puede ser realizada tratando el compuesto resultante con un agente reductor en un solvente conveniente.

Puede usarse preferentemente el hidruro de boro

(borohidruro de sodio, y lo similar), hidruros de aluminio (el hidruro de aluminio litio, hidruro de diisobutilaluminio, y lo similar) como agente reductor.

(35) El compuesto en donde R^{10} es un grupo aromático sustituido por un grupo ciano, que opcionalmente posee independientemente uno a tres heteroátomos seleccionados del átomo de oxígeno, átomo de azufre y átomo de nitrógeno (más adelante en la presente, denominado "un grupo aromático"), puede ser preparado por cianación de un compuesto en donde R^{10} es un grupo aromático sustituido por un átomo halógeno.

La cianación pueden ser realizada de la misma manera como en el PROCEDIMIENTO 4-(E).

(3b) El compuesto en donde R^1 es un átomo de hidrógeno puede ser preparado por tratamiento ácido o reducción de un compuesto en donde R^1 es un grupo terc-butoxicarbonilc o un grupo benciloxicaxbonilo.

El tratamiento ácido puede ser realizado de la misma manera como en (27) y la reducción puede ser realizada de la misma manera como en (23).

(37) El compuesto en donde R^1 es un grupo alcoxicarbonilo opcionalmente sustituido, o un grupo carbamoilo opcionalmente sustituido puede ser preparado haciendo reaccionar un compuesto en donde R^1 es un átomo de hidrógeno con un agente de carbonilación, o un alcohol conveninente o un amina conveninente en un solvente adecuado.

La reacción puede ser realizada de la misma manera como en (10).

(38) El compuesto que posee un grupo amino como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo carboxilo como sustituyente en R^5 bajo la condición de reacción de reestructuración de Curtius.

La reacción de reestructuración de Curtius puede ser realizada usando un agente de azidación convencional (por ejemplo, difenilfosforilazida) en un solvente conveniente en presencia de una base.

La reacción también puede ser realizada agregando un alcohol para proveer un compuesto que posee un grupo alcoxicarbonilamino opcionalmente sustituido como sustituyente en R^5, seguido por eliminación del grupo alcoxicarbonilo.

La eliminación del grupo alcoxicarbonilo puede ser realizada en la misma manera convencional como un tratamiento ácido o una reducción que depende del tipo de grupo alcoxicarbonilo a ser eliminado. El tratamiento ácido puede ser realizado de la misma manera como en (27) y la reducción puede ser realizada de la misma manera como en (23).

(39) El compuesto que posee un grupo hidroxilo como sustituyente en R^5 puede ser preparado reduciendo catalíticamente un compuesto que posee un grupo benciloxilo como sustituyente en R^5. La reducción puede ser realizada de

la misma manera como en (23).

(40) El compuesto que posee un grupo oxo como sustituyente en 12 puede ser preparado oxidando un compuesto que posee un grupo hidroxilo como sustituyente en R^5.

La oxidación puede ser realizada usando un agente oxidante en un solvente conveniente.

Un agente oxidante convencional puede ser usado como agente oxidante, tal como el complejo de cromato-piridina, clorocromato de piridinio, bicromato de piridinio, reactivo Dess-Martin (1,1,1-tris(acetoxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona), dimetilsulfóxido, y lo similar.

(41) El compuesto que contiene un grupo alcoxilo opcionalmente sustituido como sustituyente en R^5 puede ser preparado por la alquilación del compuesto que contiene un grupo hidroxilo como sustituyente en R^5.

La alquilación puede ser realizada usando un compuesto correspondiente de la misma manera como en el PROCEDIMIENTO 4-(A).

(42) El compuesto que posee un grupo alcanoilamino opcionalmente sustituido como sustituyente en R^5 puede ser preparado condensando un compuesto que posee un grupo amino como sustituyente en R^5 con ácido carboxílico correspondiente o un derivado reactivo del mismo.

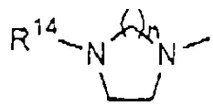
La condensación con ácido carboxilico correspondiente puede ser realizada preferentemente en un solvente

conveniente en presencia de un agente de condensación. La reacción puede ser realizada de la misma manera como en (13).

Adicionalmente, la condensación con el derivado reactivo del ácido carboxílico correspondiente puede ser realizada en un solvente o diluyente conveniente en presencia o ausencia de una base.

El derivado reactivo incluye un haluro ácido, un anhídrido ácido, un éster activado, una amida activada, y lo similar.

(43) El compuesto que posee un grupo de la fórmula:



en donde R^{14} es un grupo alcanoilo sustituido por un grupo hidroxilo o un grupo alcoxilo opcionalmente, y n posee el mismo significado como el definido anteriormente como sustituyente en R^5 puede ser preparado por condensación de un compuesto de un grupo de la fórmula:



en donde los símbolos tienen el mismo significado como el definido anteriormente como sustituyente en R^5 con un ácido carboxílico correspondiente o un derivado reactivo del mismo.

La reacción puede ser realizada de la misma manera como

en (42).

(44) El compuesto que posee un grupo maleimida como sustituyente en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo amino como sustituyente en R^5 con un anhídrido maleico. La reacción puede ser realizada en un solvente conveniente.

(45) El compuesto que posee un grupo alquilo sustituido por un grupo piridilo y un grupo hidroxilo como sustituyentes en R^5 puede ser preparado haciendo reaccionar un compuesto que posee un grupo alquilo sustituido por un grupo piridilo en el cual el átomo de nitrógeno es oxidado como sustituyente en R^5 con un anhídrido trifluoracético. La reacción puede ser realizada en un solvente conveniente.

(46) El compuesto que posee un átomo halógeno como sustituyente en R^5 puede ser preparado tratando un compuesto que posee un grupo hidroxilo como sustituyente en R^5 con un agente de halogenación.

Como el agente de halogenación, puede usarse preferentemente un agente de halogenación convencional que incluye cloruro de tionilo, oxicloruro de fósforo, así como tetrahaluro de carbono (por ejemplo, tetracloruro de carbono, tetrabromuro de carbono, y lo similar), y fosfinas (por ejemplo, trifenilfosfina, y lo similar).

(47) El compuesto que posee un grupo cianoalquilo como sustituyente en R^5 puede ser preparado por reducción de un

compuesto que posee un grupo cianoalquenilo como sustituyente en R^5.

La reducción puede ser realizada tratando un compuesto de comienzo con un agente reductor o por reducción catalítica en un solvente conveniente.

Cualquier agente reductor puede ser usado con la condición que reduzca sólo un enlace doble sin afectar un grupo ciano. Por ejemplo, puede ser usado preferentemente hidruro de bis(2-metoxietoxi)aluminio de sodio en presencia de un bromuro de cobre.

La reducción catalítica puede ser realizada de la misma manera como en (23).

(48) El compuesto que posee un grupo hidroxialquilo como sustituyente en R^5 puede ser preparado reduciendo un compuesto que posee un grupo formilo como sustituyente en R^5.

La reducción puede ser realizada tratando un compuesto de comienzo con un agente reductor en un solvente conveniente.

La reacción puede ser realizada de la misma manera como en el procedimiento para reducir en (34).

(49) El compuesto en donde R^7 es un grupo hidroxilo puede ser preparado por desmetilación de un compuesto en donde R^7 es un grupo metoxilo.

La desmetilación pueden ser realizada tratando un compuesto de comienzo con un agente de desmetilación en un solvente conveniente.

El agente convencional incluye yoduro de trimetilsililo, ácido bromhídrico/ácido acético, tribromuro de boro, ácido sulfúrico concentrado, y lo similar puede ser usado como agente de desmetilación.

(50) El compuesto en donde R^7 es un grupo alcoxilo opcionalmente sustituido puede ser preparado por alquilación de un compuesto en donde R^7 es un grupo hidroxilo.

La alquilación puede ser realizada de la misma manera como el PROCEDIMIENTO 4-(A).

(51) El compuesto en donde R^7 es un grupo alquilsulfoniloxilo opcionalmente sustituido puede ser preparado por alquilsulfonilación de un compuesto en donde R^7 es un grupo hidroxilo.

La alquilsulfonilación puede ser realizada haciendo reaccionar un haluro de alquilsulfonilo correspondiente o un anhídrido alquilsulfónico correspondiente en un solvente conveniente en presencia o ausencia de una base.

(52) El compuesto en donde R^7 es un grupo ciano puede ser preparado por cianación de un compuesto en donde R^7 es un grupo alquilsulfoniloxilo opcionalmente sustituido.

La cianación pueden ser realizada de la misma manera como el PROCEDIMIENTO 4-(E).

(53) El compuesto en donde R^7 es un grupo aminoalquilo puede ser preparado por reducción de un compuesto en donde R^7 es un grupo ciano.

La reducción puede ser realizada de la misma manera como en (6).

(54) El compuesto en donde R^7 es un grupo alquilo puede ser preparado por alquilación de un compuesto en donde R^7 es un grupo alquilsulfoniloxilo opcionalmente sustituido.

La alquilación puede ser realizada haciendo reaccionar alquil aluminio en presencia de un catalizador de paladio, un catalizador de plata, y un catalizador de cobre en un solvente conveniente.

Puede usarse preferentemente tetrakis(trifenilfosfina)paladio como catalizador de paladio, carbonato de plata como catalizador de plata, cloruro de cobre (I) como el catalizador de cobre.

(55) El compuesto que posee un grupo imidazolinilo o un grupo oxazolinilo como sustituyente en R^5 puede ser preparado por (i) hacer reaccionar un compuesto que contiene un grupo ciano como sustituyente en R^5 con un alcohol conveninete en presencia de un ácido en un solvente o diluyente conveniente para proveer un compuesto que contiene un grupo alcoxicarbonimidoilo como sustituyente en R^5, y (ii) hacer reaccionar el compuesto que contiene un grupo alcoxicarbonimidoilo como sustituyente en R^5 con 2-aminoetanol o etilen diamina en un solvente o diluyente conveniente.

(56) El compuesto que posee un grupo carboxilo como sustituyente en R^1 puede ser preparado por (i) oxidar un

compuesto que contiene un grupo hidroxialquilo como sustituyente en R^1 de la misma manera que en (40) para proveer un compuesto que contiene un grupo oxo como sustituyente en R^1, y (ii) oxidar el compuesto que contiene el grupo oxo como sustituyente en R^1.

La oxidación para la segunda etapa puede ser realizada utilizando un agente de oxidación en un solvente conveniente. Pueden ser utilizados preferiblemente como agente de oxidación clorito de sodio, óxido de plata(I), peryodato de sodio y lo similar.

(57) El compuesto que posee un grupo carboxilo como sustituyente en R^1 puede ser preparado directamente oxidando un compuesto que contiene un grupo hidroxialquilo como sustituyente en R^1.

La oxidación puede ser realizada utilizando como agente de oxidación un reactivo de Jones, permanganato de potasio, y lo similar.

(58) El compuesto en donde R^1 es átomo de hidrógeno puede ser realizado por tratamiento de un compuesto en donde R^1 es grupo etoxicarbonilo con un haluro de sililo o una base. El yoduro de trimetilsililo puede ser utilizado preferiblemente como el haluro de sililo. Preferiblemente como la base puede ser utilizado hidróxido de sodio.

En cada procedimiento para preparar un compuesto de la fórmula (I) descripto anteriormente, cuando se necesita

protección de un grupo funcional contenido en cualquier compuesto, la protección puede ser realizada en una manera convencional ad libitum. La declaración general relacionada a los grupos protectores y su uso se provee por Greene, "Protective Groups in Organic Synthesis", John Wiley e Hijos, Nueva York, 1991.

Cuando un grupo amino es protegido por un grupo benciloxicarbonilo, el grupo protector puede ser eliminado por una reducción catalítica bajo hidrógeno en un solvente conveniente.

Cuando un grupo hidroxilo es protegido por un grupo bencilo, el grupo protector también puede ser eliminado de una manera similar por una reducción catalítica según lo anterior.

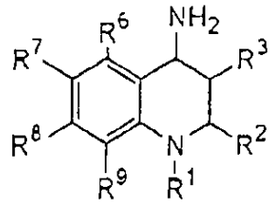
Cuando un grupo amino es protegido por un grupo t-butoxicarbonilo, el grupo protector puede ser eliminado tratando un compuesto de comienzo con un ácido (por ejemplo, ácido clorhídrico, ácido toluensulfónico, ácido trifluoracético, y lo similar) en un solvente conveniente.

Cuando un grupo hidroxilo es protegido por un grupo tetrahidropiranilo, el grupo protector también puede ser eliminado tratando un compuesto de comienzo como se hizo anteriormente con un ácido de una manera similar.

Las reacciones (1) a (58) para conversión de R^1, R^5, R^7, ó R^{10} también pueden ser aplicadas de la misma manera para

conversión de otros sustituyentes del presente compuesto (I) según sea apropiado.

El compuesto de comienzo (II) es un nuevo compuesto, y puede ser preparado condensando un compuesto de la fórmula (X):



(X)

en donde los símbolos tienen el mismo significado como el definido anteriormente con un compuesto de la fórmula (XI):

R^5-Z^4 (XI)

en donde Z^4 es un grupo de partida y R^5 tiene el mismo significado como el definido anteriormente.

Como el grupo de partida, un átomo halógeno incluye átomo de cloro, átomo de bromo, átomo de iodo, y un grupo sulfoniloxilo sustituido incluye grupo metansulfoniloxilo, grupo p-toluensulfoniloxilo, se usa preferentemente grupo trifluorometansulfoniloxilo.

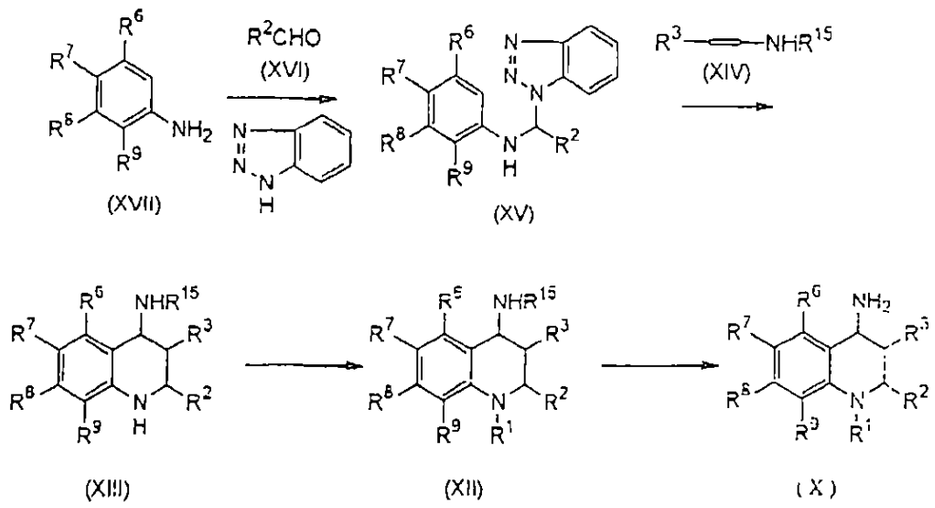
La reacción puede ser realizada en un solvente conveniente (por ejemplo, 1,4-dioxano, dimetilformamida, 1,3-dimetilimidazolidinona, y lo similar) en presencia o ausencia de una base (por ejemplo, diisopropiletilamina, y lo similar) desde la temperatura ambiente hasta bajo calentamiento.

La reacción también puede ser realizada agregando un catalizador de paladio (por ejemplo,

tris(dibencilidenacetona)dipaladio) y una fosfina [por ejemplo, trifenilfosfina, tributilfosfina, o 2-(di-terc-butilfosfino)bifenilo] a la temperatura ambiente en presencia de una base (por ejemplo, terc-butoóido de sodio), si se desea.

Un compuesto de la fórmula (X) puede ser preparado según el método descripto en WO00/17165 o US 6.313.142.

Alternativamente, el compuesto (X) puede ser preparado según el esquema siguiente:



en donde R^{15} es un grupo protector para el grupo amino y los otros símbolos tienen el mismo significado como el definido anteriormente.

Un grupo protector convencional incluye un grupo benciloxicarbonilo puede ser usado como grupo protector para el grupo amino. Adicionalmente, un compuesto ópticamente activo (X) puede ser preparado protegiendo el grupo amino con

un grupo protector ópticamente activo para grupo amiro (por ejemplo, un grupo benciloxicarbonilo α-sustituido ópticamente activo que posee un centro quiral en la posición benci.o, tal como grupo α-metilbenciloxicarbonilo), resolviéndo el diastereómeros en el procedimiento para preparación de compuesto (XII) ó compuesto (XIII), y eliminando el grupo protector.

Un compuesto de la fórmula (XV) puede ser preparado haciendo reaccionar benzotriazol, un compuesto de la fórmula (XVI) y un compuesto de la fórmula (XVII) en un solvente conveniente (por ejemplo, tolueno) a la temperatura ambiente.

Un compuesto de la fórmula (XIII) puede ser preparado haciendo reaccionar un compuesto de la fórmula (XIV) con un compuesto de la fórmula (XV) en presencia de un catalizador ácido (por ejemplo, un ácido orgánico que incluye ácido p-toluensulfónico, ácido acético, ácido metansulfónico, o ácido Lewis que incluye el complejo trifluoruro dietiléter de boro, tetracloruro de titanio, cloruro de aluminio) en un solvente conveniente (por ejemplo, tolueno, tetrahidrofurano, cloruro de metileno, y lo similar) bajo calentamiento o a la temperatura ambiente (por ejemplo, de 0°C a 150°C, preferentemente de 25°C a 120°C).

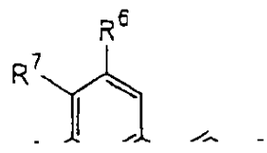
Un compuesto de la fórmula (XII) puede ser preparado por alcanoilación, alcoxicarbonilación, alquilación, y lo similar

desde un compuesto de la fórmula (XIII) según sea apropiado.

Un compuesto de la fórmula (X) puede ser preparado eliminando un grupo protector para el grupo amino de un compuesto de la fórmula (XII). La eliminación del grupo protector puede ser realizada de una manera convencional inclusive tratamiento ácido, tratamiento base, reducción, y lo similar dependiendo del tipo de grupo protector. Cuando es utilizado un grupo benciloxicarbonilo o un grupo benciloxicarbonilo α-sustituido, los mismos pueden ser eliminados por una reducción catalítica en un solvente conveniente (por ejemplo, etanol, metanol, tetrahidrofurano, ácido acético, y lo similar) bajo hidrógeno. La eliminación de un grupo protector para el grupo amino de un compuesto de la fórmula (XIII) puede ser realizada de la misma manera como la eliminación del grupo protector para el grupo amino de un compuesto de fórmula (XII).

Cuando un grupo protector ópticamente activo tal como el grupo benciloxicarbonilo α-sustituido es usado como grupo protector para el grupo amino, la resolución de un diastereómero puede ser realizada de una manera convencional tal como recristalización o cromatografía en columna.

Un compuesto de la fórmula (XIII) también puede ser preparado haciendo reaccionar un compuesto de la fórmula (XIV) con un compuesto de la fórmula (XVIII).



(XVIII)

Esta reacción puede ser realizada de la misma manera como la reacción de un compuesto de la fórmula (XIV) con un compuesto de la fórmula (XV).

Adicionalmente, los sustituyentes respectivos R^1, R^5, R^6, R^7, R^8 y R^9 pueden ser convertidos en un sustituyente conveniente de acuerdo con cualquiera de los procedimientos del PROCEDIMIENTO 4-(A) a (K) y de (1) a (58).

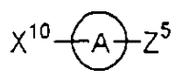
Un compuesto de la fórmula (IV) puede ser preparado por condensación de un compuesto de la fórmula (X) con un compuesto de la fórmula (III)

$$R^{10}-R^4-Z^1 \qquad (III)$$

en donde los símbolos tienen el mismo significado como el definido anteriormente.

La condensación puede ser realizada de la misma manera como se describe precedentemente en WO00/17165 o PROCEDIMIENTO 1.

Un compuesto de fórmula (IX) puede ser preparado por condensación de un compuesto de la fórmula (IV) con un compuesto de la fórmula:



en donde Z^5 es un grupo de partida y los otros símbolos tienen el mismo significado como el definido precedentemente.

Como grupo de partida, puede usarse preferentemerte un átomo halógeno que incluye el átomo de cloro, átomo de bromo, átomo de yodo; un grupo sulfoniloxilo sustituido que incluye el grupo metansulfoniloxilo, grupo p-toluensulfoniloxilo, grupo trifluorometansulfoniloxilo.

La condensación puede ser realizada de la misma manera como en uno de dichos compuestos (X) con el compuesto (XI).

Adicionalmente, el compuesto de la fórmula (IX) en donde el anillo A es un grupo tetrazolilo y X^{10} es un átomo de hidrógeno puede ser preparado haciendo reaccionar un compuesto de la fórmula (V) con un alquil azida de metal. La reacción puede ser realizada de la misma manera como en (15) descripto precedentemente.

Adicionalmente, el compuesto de fórmula (IX) en donde X^{10} es un grupo hidroxilo puede ser realizado por (I) hacer reaccionar un compuesto en donde X^{10} es un átomo halógeno con diboro o borano para proveer un compuesto en donde X^{10} es un éster borónico con peróxidos.

Pueden ser utilizados preferentemente como los peróxidos una solución de peróxido de hidrógeno, ácido m-cloroperbenzoico, o OXONE^{MR} (fabricado por DuPont).

Muchos de los materiales de comienzo y reactivos para la preparación del compuesto mencionado de la fórmula I son

tanto comercialmente disponibles como descriptos en las literaturas o pueden ser preparados fácilmente por un método que se describe en las literaturas o generalmente es usado en la síntesis orgánica.

Como es utilizado en la presente, el "3,4-dihidro-2H-quinolina" representa la misma estructura de "1,2,3,4-tetrahidroquinolina".

Experimento

La actividad inhibitoria de compuestos de la presente invención contra CETP fue probada en este experimento.

Preparación de la Microemulsión aceptadora

Una solución de 1-palmitoil-2-oleoil-sn-glicero-3-fosfocolina (3,5 mg), oleato de colesterilo (3mg) y trioleina (0,7 mg) en cloroformo fue mezclada y el lípido fue secado por aire bajo gas nitrógeno para eliminar el solvente. Fue agregado entonces 1,4-dioxano (0,25 ml) y la mezcla fue agitada para disolución. La solución de lípido de resultante (0,2 ml) fue inyectada despacio bajo la superficie de la solución amortiguadora Tris-salina-EDTA(TSE) [10mM Tris/HCl (pH 7,4), 0,15M NaCl, 2mM ETA] (10 mL) con jeringa Hamilton, mientras fue sonificada en baño de hielo. Después de 1 hora de sonificación en el baño de hielo, la solución se mantuvo a 4 °C.

Preparación de la Microemulsión donadora

Una solución de huevo PC (fosfatidilcolina) (0,33 mg) y

BODIPY-CE (0,62 mg) fue mezclada en cloroformo. Después de eliminar el solvente secando al aire el lípido bajo gas nitrógeno, solución amortiguadora de TSE (3 ml) fue agregada y la solución sonificada en el baño de hielo. Esta solución fue filtrada para esterilizarla a través de filtros de 0,22 µm y fue mantenida a 4 °C.

Actividad inhibitoria contra CETP in vitro

Fue preparada una solución de prueba utilizando dimetilsulfóxido como solvente. El plasma de un voluntario saludable fue diluido a 0,64% con solución amortiguadora de TSE, y a la solución de plasma resultante (187 µl) fue agregada a una solución de prueba (3 µl) o el solvente solamente seguido por incubación a 37 °C durante 24 horas. Después del agregado de solución amortiguadora de TSE (10 µL) conteniendo una microemulsión donadora al 5% y microemulsión aceptadora al 5%, la mezcla fue incubada a 37 °C durante 3 horas. Antes y después de la incubación, la intensidad de fluorescencia fue medida en Ex.550nm/Em.600nm. La actividad de CETP fue definida como la diferencia entre las mediciones obtenidas antes de la incubación y después de la incubación.. La proporción decreciente de diferencia en la muestra fue definida como la proporción de inhibición de activicad de CETP. El IC_{50} para cada muestra fue calculado desde la proporción de inhibición de actividad de CETP.

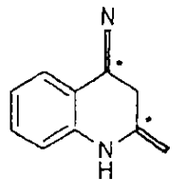
Resultados

Ejemplo No.	IC_{50} (nM)
1	0,17
16	4,2
127	0,89
174	0,23
198	0,66
231	0,53
275	0,18

EJEMPLOS

La presente invención se ilustra en más detalle por los Ejemplos y Ejemplos de referencia, pero la presente invención no debe interpretarse como limitada por los mismos.

En los Ejemplos, los compuestos que poseen una estructura de fórmula:



indica que la configuración de los mismos es de (2R*,4S*). Además, Me indica un grupo metilo.

Ejemplo 1

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3 g) y 5-bromo-2-cloropirimidina (3,7 g) fueron disueltos en N,N-dimetilformamida (30 ml), y la mezcla fue agitada a 150°C durante 5 horas. La solución de reacción fue enfriada la temperatura ambiente, y fueron agregados a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio y

acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 8:1→4:1) para dar etil éster de ácido (2R,4S)-4-(5-bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,2 g). MS (m/z): 473/475 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,2 g) fue disuelto en N,N-dimetilformamida (20 ml), y fueron agregados a los mismos hidruro de sodio (62,7%, 223 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. A la mezcla fue agregado bromuro de 3,5-bis(trifluorometil)bencilo (1,3 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante una hora. Se agregan una solución salina saturada y acetato de etilo a la mezcla, y la capa orgánica fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 10:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,75 g). MS (m/z): 699/701 $[M+H]^+$

(3) etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il))-amiro-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (94 mg), tris(dibencilidenacetona)dipaladio (2,5 mg), terc-butóxido de sodio (19 mg), 2-(di-terc-butilfosfino)bifenilo (3 mg), morfolina (18 µl) fue disuelto en tolueno (1 ml), y la mezcla fue agitada a la temperatura ambiente bajo la de nitrógeno durante 60 horas. Fue agregado a la solución de reacciónel ácido acético, y fueron agregados a los mismos el agua y el acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 19:1→3:2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (40 mg). MS (m/z): 706 $[M+H]^+$

Ejemplos 2-6

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 1-(3) para dar los compuestos como los enumerados en la Tabla 1.

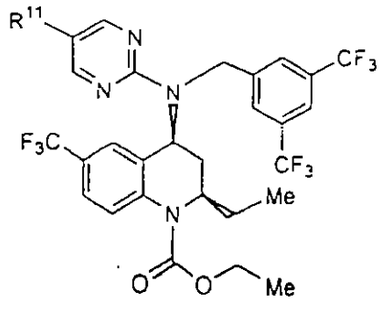
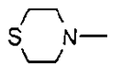
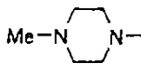
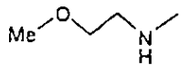
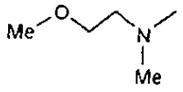
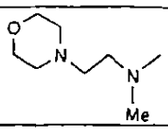


Tabla 1

Ejemplo	R^{11}	Propiedades físicas, etc.
2		MS (m/z): 722 $[M+H]^+$
3		MS (m/z): 719 $[M+H]^+$
4		MS (m/z): 694 $[M+H]^+$
5		MS (m/z): 708 $[M+H]^+$
6		MS (m/z): 763 $[M+H]^+$

Ejemplo 7

Etil éster de ácido (2R,4S)-4-({[3,5-Bis(trifluorometil)bencil]-[5-(tiomorfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (75 mg) fue disuelto en cloroformo (3 ml), y fueron agregados a los mismos ácido m-cloroperbenzoico (25 mg), y la mezcla fue agitada toda la noche a la temperatura ambiente. Fue agregada a la solución de reacciónagua y cloroformo, y la capa orgánica fue lavada con una solución salina saturada, secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice;

cloroformo:acetona = 10:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(1-oxotiomorfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (34 mg). MS (m/z): 738 $[M+H]^+$

Ejemplo 8

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (250 mg) y diclorobis(tri-o-tolilfosfina)paladio (5,9 mg) fue disuelto en tolueno (2 ml), y la mezcla fue calentada a 100°C bajo atmósfera de nitrógeno. Fue agregado a la solución de reacción(dimetilamino)trimetilestaño (118 mg), y la mezcla fue agitada durante 2 horas. A la mezcla se le permite enfriar a temperatura ambiente, y la solución de reacción fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo = 5:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-dimetilaminopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (18 mg). MS (m/z): 664 $[M+H]^+$

Ejemplo 9

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (600 mg)

y 2-cloro-5-propilpirimidina (1,5 g) fueron disueltos en 1,3-dimetilimidazolidinona (10 ml), y la mezcla fue agitada a 135°C durante 72 horas. La solución de reacción fue enfriada la temperatura ambiente, y fueron agregados a los mismos el agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 6:1→4:1) para dar etil éster de ácido (2R,4S)-2-etil-4-(5-propilpirimidin-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (250 mg). MS (m/z): 437 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-2-etil-4-(5-propilpirimidin-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (240 mg) y bromuro de 3,5-bis(trifluorometil)bencilo (337 mg) fueron disueltos en N,N-dimetilformamida (3 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 32 mg) a la temperatura ambiente, y la mezcla fue agitada a la misma temperatura durante 2 horas. Fue agregado a la solución de reacción el ácido acético, y fueron agregados agua y acetato de etilo a los mismos. La capa orgánica fue secada sobre sulfato del magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo =49:1→7:3) para dar etil éster de

ácido (2R,4S)-4-{[3,5,-bis(trifluorometil)bencil]-(5-propilpirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (130 mg). MS (m/z): 663 $[M+H]^+$

Ejemplo 10

A etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1 g) fue agregado N,N-dimetilformamida (10 ml), tetrakis(trifenilfosfina)paladio (una cantidad catalítica), y cianuro de zinc (176 mg), y la mezcla fue agitada a 110°C bajo atmósfera de nitrógeno durante 4 horas. La solución de reacción fue enfriada la temperatura ambiente, y fueron agregados a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 10:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-cianopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (760 mg). MS (m/z): 646 $[M+H]^+$

Ejemplo 11

Etil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-(5-cianopirirnidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en etanol (3 ml), y fueron agregados a los mismos una cantidad catalítica de níquel Raney, y la mezcla fue agitada a la temperatura ambiente de noche bajo atmósfera de hidrógeno. El catalizador eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo es purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 1:1) para dar etil éster de ácido (2R,4S)-4-{(5-aminometilpirimidin-2-il)-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (142 mg). MS (m/z):650 $[M+H]^+$

Ejemplo 12

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-aminometil-pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (92 mg) y una cantidad en exceso de trietilamina fue disuelto en cloruro de metileno (2 ml), y fueron agregados a los mismos una cantidad en exceso de cloruro de N,N-dimetilsulfamoilo bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 2 horas, y a la solución de reacción se agregan una solución salina saturada y acetato de etilo. La capa orgánica fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo

resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→67:33) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil)-[5-(N,N-dimetilsulfamoil)aminometilpirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (54 mg). MS (m/z): 757 $[M+H]^+$

Ejemplo 13

El ácido acético (88 µl) fue disuelto en tolueno (3 ml), y fueron agregados a los mismos trietilamina (236 µl) y azida de difenilfosforilo (466 µl). La mezcla fue agitada a 70 °C durante 1,5 hora. Fue agregado a la solución de reacciónetil éster de ácido (2R,4S)-4-{(5-aminometilpirimidin-2-il)-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg), y la mezcla fue agitada a la misma temperatura durante 4 horas. A la mezcla se permite enfriar a la temperatura ambiente, y a la solución de reacción se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo = 1:2) para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-{5-[(3-

metilureido)metil]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (63 mg). MS (m/z): 707 $[M+H]^+$

Ejemplo 14

4-(2-Aminoetil)morfolina (100 mg) fue disuelto en tetrahidrofurano (3 ml), y fueron agregados a los mismos N,N'-carbonildiimidazol (125 mg), y la mezcla fue agitada a 70°C durante una hora. A la solución de reacción se agrega etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-aminometilpirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg), y la mezcla fue agitada a la misma temperatura durante 4 horas. La mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; acetato de etilo) para dar etil éster de ácido (2R,4S)-4-({[3,5-bis(trifluorometil)bencil]-[5-[3-(2-morfolin-4-iletil)ureidometil]pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (118 mg). MS (m/z): 806 $[M+H]^+$

Ejemplo 15

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirirnidin-2-1)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg), acetato de paladio (12 mg), 1,1'-bis(difenilfosfino)ferroceno (55 mg), alcohol bencílico (970 mg) y trietilamina (625 µl) fueron disueltos en N,N-dimetilformamida (1 ml), y la mezcla fue agitada a la temperatura ambiente bajo atmósfera de monóxido de carbono durante 3 minutos. A continuación, la mezcla fue calentada a 90°C y fue agitada toda la noche. La solución de reacción fue enfriada la temperatura ambiente, y fueron agregados a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 24:1→3:1) para dar etil éster de ácido (2R,4S)-4-{(5-benciloxicarbonilpirimidin-2-il)-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (250 mg). MS (m/z): 755 $[M+H]^+$

Ejemplo 16

Etil éster de ácido (2R,4S)-4-{(5-Benciloxicarbonilpirimidin-2-il)-[3,5-bis(trifluoro-

metil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (220 mg) fue disuelto en una mezcla de metanol (2 ml) y tetrahidrofurano (6 ml), y fueron agregados a los mismos 10% paladio-carbono (100 mg), y la mezcla fue agitada a la temperatura ambiente bajo atmósfera de hidrógeno durante 30 minutos. El catalizador (10% paladio carbono) fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; acetato de etilo) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-carboxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (178 mg). MS (m/z): 665 $[M+H]^+$

Ejemplo 17

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-carboxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) y una cantidad en exceso de hidrato de 1-hidroxibenzotriazol fue disuelto en N,N-dimetilformamida (5 ml), y fueron agregados a los mismos una cantidad en exceso de hidrocloruro de 1-etil-3-(3-dimetilaminopropil)carbodiimida, y la mezcla fue agitada a la temperatura ambiente durante 10 minutos. Fue agregado a la solución de reacciónhidrocloruro de glicin terc-butil éster (50 mg) y una cantidad en exceso de trietilamina, y la mezcla

fue agitada a la temperatura ambiente durante 10 minutos. A la solución de reacción fueron agregaas una solución de ácido cítrico acuosa y acetato de etilo, y la capa orgánica fue lavada con una solución acuosa saturada de carbonato hidrógeno de sodio, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-terc-butoxicarbonilmetilcarbamoilpirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico.

Entonces, a la mezcla se agrega 4N ácido clorhídrico en 1,4-dioxano (2 ml) a la temperatura ambiente, y la mezcla fue agitada toda la noche. La solución de reacción fue concentrada bajo presión reducida, y el residuo concentrado fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 1:1→cloroformo:metanol = 19:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-carboximetilcarbamoilpirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (13 mg). MS (m/z): 722 $[M+H]^+$

Ejemplo 18

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-

etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg), bencil éster de ácido acrílico (125 mg), tris(dibencilidenacetona)dipaladio (12 mg), diisopropiletilamina (90 µl), tetrafluoroborato de triterc-butilfosfonio (7,5 mg) fue disuelto en 1,4-dioxano (3,5 ml), y la mezcla fue agitada bajo atmósfera de nitrógeno a la temperatura ambiente durante 3 días. A la solución de reacción se agregan una solución de ácido cítrico acuosa y acetato de etilo, y la capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 97:3→13:7) para dar etil éster de ácido (2R,4S)-4-{[5-(2-benciloxicarbonilvinil)pirimidin-2-il]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (186 mg). MS (m/z): 781 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[5-(2-Benciloxicarbonilvinil)pirimidin-2-il]-{3,5-bis-(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (180 mg) fue disuelto en una mezcla de metanol (5 ml) y tetrahidrofurano (10 ml), y fueron agregados a los mismos 10 % paladio carbono (300 mg). La mezcla fue agitada a la temperatura ambiente bajo

atmósfera de hidrógeno durante 3 horas. El catalizador fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-carboxietil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (40 mg). MS (m/z): 693 $[M+H]^+$

Ejemplo 19

Etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-(5-cianopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (880 mg), azida de sodio (886 mg) y cloruro de amonio (729 mg) fueron disuelto en N,N-dimetilformamida (5 ml), y la mezcla fue agitada a 100°C durante 4 horas. La mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(tetrazol-5-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (920 mg). MS (m/z): 689 $[M+H]^+$

Ejemplo 20

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-[5-(tetrazol-5-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico (150 mg), carbonato de potasio (60 mg), y una cantidad en exceso de yoduro de metilo fue disuelto en N,N-dimetilformamida (2 ml), y la mezcla fue agitada a 50°C durante 4 horas. La mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo=9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-{5-(2-metil-2H-tetrazol-5-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (107 mg). MS (m/z): 703 $[M+H]^+$

Ejemplos 21-22

Los compuestos de comienzo correspondientes fueron tratados en una manera similar al Ejemplo 20 para dar los compuestos como los enumerados en Tabla 2.

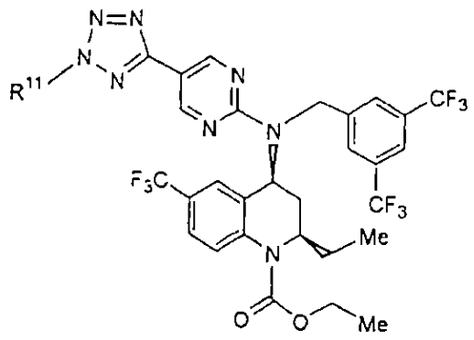
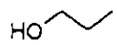
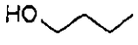


Tabla 2

Ejemplo	R^{11}	Propiedades físicas, etc.
21		MS (m/z): 733 $[M+H]^+$
22		MS (m/z): 747 $[M+H]^+$

Ejemplo 23

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(tetrazol-5-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (127 mg), 4-(2-hidroxietil)morfolina (35 µl), y trifenilfosfina (76 mg) fue disuelto en tetrahidrofurano (3 ml), y a los mismos fueron agregados por gotas una solución 40% dietil éster de ácido azodicarboxílico en tolueno (113 µl) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 4 horas. A la solución de reacción se agregan agua y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue

secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo = 9:1→67:33) para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-(5-[2-(2-morfolin-4-iletil)-2H-tetrazol-5-il]pirimidin-2-il))amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (136 mg). MS (m/z): 802 $[M+H]^+$

Ejemplo 24

(1) Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il))amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,00 g) fue disuelto en 1,4-dioxano (4,0 ml), y fueron agregados a los mismos yoduro de sodio (857 mg), yoduro de cobre (27 mg) y trans-N,N'-dimetilciclohexan-1,2-diamina (43 mg), y la mezcla fue agitada toda la noche a 110 °C bajo atmósfera de nitrógeno. La mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos una solución de amonio acuosa diluída, y la mezcla se extrae con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 97:3→70:30) para dar

etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-iodopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (969 mg). MS (m/z): 747 $[M+H]^+$

(2) A etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-iodoepirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue agregado 2-metoxietanol (1,0 ml), carbonato de cesio (350 mg), yoduro de cobre (23 mg) y 1,10-fenantrolina (44 mg), y la mezcla fue agitada a 110°C durante 4 días. La mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 10:1, y gel de NH-sílice; hexano:acetato de etilo = 10:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (90 mg, MS (m/z): 695 $[M+H]^+$) y 2-metoxietil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (28 mg, MS (m/z): 725 $[M+H]^+$).

Ejemplo 25

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1 g), 6-cloronicotinonitrilo (1,76 g), diisopropiletilamina (804 µl) fue disuelto en N,N-dimetilformamida (15 ml), y la mezcla fue agitada toda la noche a 100°C. La solución de reacción fue enfriada la temperatura ambiente, y fueron agregados a los mismos una solución de ácido cítrico acuosa y acetato de etilo. La capa orgánica fue lavada con una solución salina saturado, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; cloroformo:hexano:acetato de etilo = 5:5:1) para dar etil éster de ácido (2R,4S)-4-(5-cianopiridin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (800 mg). MS (m/z): 419 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-(5-Cianopiridin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (790 mg) y bromuro de 3,5-bis(trifluorometil)bencilo (1,159 g) fue disuelto en N,N-dimetilformamida (9 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 108 mg) a la temperatura ambiente, y la mezcla fue agitada adicionalmente durante 15 minutos. A la solución de reacción se agrega ácido acético, y fueron agregados a los mismos una solución salina saturada y éter. La capa orgánica fue lavada con una solución

salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 19:1→17:8) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-cianopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (700 mg). MS (m/z): 645 $[M+H]^+$

Ejemplo 26

Etil éster de ácido (2R,4S)-4-[3,5-Bis(trifluorometil)bencil]-(5-cianopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (127 mg), azida de sodio (300 mg) y cloruro de amonio (300 mg) fueron disueltos en N,N-dimetilformamida (5 ml), y la mezcla fue agitada toda la noche a 95°C. La mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(tetrazol-5-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (128 mg). MS (m/z): 688 $[M+H]^+$

Ejemplo 27

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,5 g)

y 2-cloro-5-nitropiridina (3,795 g) fueron disueltos en 1,3-dimetilimidazolidinona (25 ml), y la mezcla fue agitada a 140°C durante 74 horas. La solución de reacción fue enfriada la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; cloroformo:hexano:acetato de etilo = 3:1) para dar (etil éster de ácido (2R,4S)-2-etil-4-(5-nitropiridin-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (991 mg). MS (m/z): 439 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-2-etil-4-(5-nitropiridin-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (980 mg) y bromuro de 3,5-bis(trifluorometil)bencilo (1,372 g) fue disuelto en N,N-dimetilformamida (10 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 171 mg) a la temperatura ambiente, y la mezcla fue agitada durante 15 minutos. Fue agregado a la solución de reacciónácido acético, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada de nuevo con agua, y la capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 49:1→13:7)

para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-nitropiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (650 mg). MS (m/z): 665 $[M+H]^+$

Ejemplo 28

(1) Etil éster de ácido (2R,4S)-4-[3,5-Bis(trifluorometil)bencil]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (600 mg) fue disuelto en etanol (5,0 ml), y fueron agregados a los mismos bromuro de cianógeno (129 mg) y carbonato de hidrógeno de sodio (283 mg), y la mezcla fue agitada a la temperatura ambiente durante 23 horas y 15 minutos. Fue agregada agua destilada a la mezcla, y la mezcla se extrajo con éter. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-ciano}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (581 mg). MS (m/z): 585 $[M+H_2O]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-ciano)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (50 mg) fue disuelto en N,N-dimetilformamida (1 ml), y fueron agregados a los mismos azida de sodio (57,2 mg) y cloruro de

amonio (47,1 mg), y la mezcla fue agitada a 100°C durante 16,5 horas. La mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos agua destilada, y la mezcla se extrajo con acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; cloroformo:metanol = 9:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(tetrazol-5-il)amino)-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (45 mg). MS (m/z): 611 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil)-(tetrazol-5-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (150 mg) fue disuelto en tetrahidrofurano (2,5 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 9,6 mg), y la mezcla fue agitada durante 10 minutos. A la mezcla fue agregado 1-bromuro de propano (23 µl), y la mezcla fue agitada durante 27 horas. El agua destilada fue agregada a la mezcla, y la mezcla se extrajo con acetato de etilo. El extracto fue lavado con una solución salina saturada, y la capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 10:1→4:1) para dar etil éster de ácido (2R,4S)-4-

{[3,5-bis(trifluorometil)bencil]-(2-propil-2H-tetrazol-5-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (26 mg). MS (m/z): 653 $[M+H]^+$

Ejemplos 29-30

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 28-(3) para producir de ésta manera los compuestos como los enumerados en la Tabla 3.

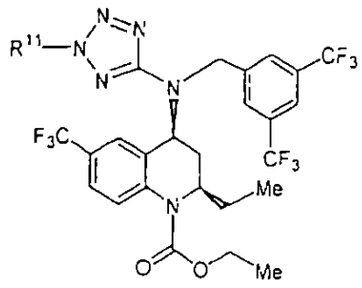
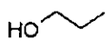
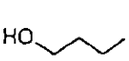


Tabla 3

Ejemplo	R^{11}	Propiedades físicas etc.
29		MS (m/z): 655 $[M+H]^+$
30		MS (m/z): 669 $[M+H]^+$

Ejemplo 31

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(tetrazol-5-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) fue disuelto en N,N-dimetilformamida (1 ml), y fueron agregados a los mismos metil éster de ácido 3-bromopropionico (103,6 µl), trietilamina (2 ml) y una cantidad catalítica de yoduro de potasio, y la mezcla fue agitada a 70°C durante 48

horas. Fue agregada agua destilada a la mezcla, y la mezcla fue extractada con éter. El extracto fue secado sobre sulfato de magnesio, y fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorornetil)bencil]-[2-(2-metoxicarboniletil]-2H-tetrazol-5-il}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (581 mg). MS (m/z): 697 $[M+H)^+$

Ejemplos 32-34

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 31 para dar los compuestos enumerados en la Tabla 4.

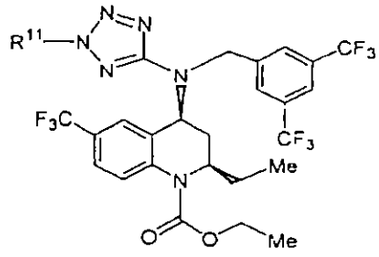
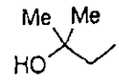
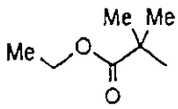
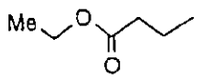


Tabla 4

Example	R^{11}	Physical properties, etc.
32		MS (m/z): 683 $[M+H]^+$
33		MS (m/z): 725 $[M+H]^+$
34		MS (m/z): 697 $[M+H]^+$

Ejemplo 35

Etil éster de ácido (2R,4S)-4- [3,5-Bis(trifluorometil)bencil]-(tetrazol-5-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en tetrahidrofurano (5 ml), y fueron agregados a los mismos 2-dimetilaminoetanol (50 µl), una solución al 40% de azodicarboxilato de dietilo en tolueno (220 µl) y trifenilfosfina (131,1 mg), y la mezcla fue agitada a temperatura ambiente durante 1,5 horas. Fue agregada agua destilada a los mismos, y la mezcla fue extraída con acetato de etilo. El extracto fue secado sobre sulfato de magnesio, y fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo =9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(2-dimetilaminoetil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (155 mg). MS (m/z): 682 $[M+H]^+$

Ejemplos 36-45

Los compuestos de comienzo correspondientes fueron tratados de manera similar al del Ejemplo 35 para dar los compuestos enumerados en la Tabla 5.

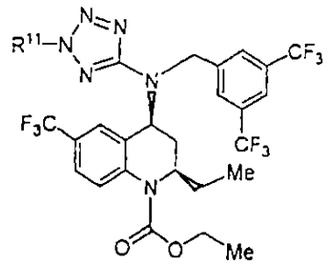
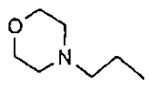
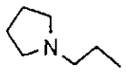
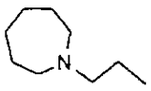
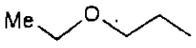
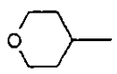
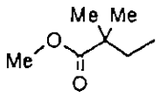
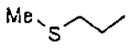
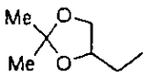
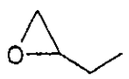
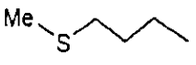


Tabla 5

Ejemplo	R^{11}	Propiedades físicas, etc.
36		MS (m/z): 724 $[M+H]^+$
37		MS (m/z): 708 $[M+H]^+$
38		MS (m/z): 736 $[M+H]^+$
39		MS (m/z): 683 $[M+H]^+$
40		MS (m/z): 695 $[M+H]^+$
41		MS (m/z): 725 $[M+H]^+$
42		MS (m/z): 685 $[M+H]^+$
43		MS (m/z): 725 $[M+H]^+$
44		MS (m/z): 667 $[M-H]^-$
45		MS (m/z): 699 $[M+H]^+$

Ejemplo 46.

Etil éster de ácido (2R,4S)-4-{[3,5-

bis(triflourometil)bencil]-[2-(2-metoxicaronil-2-metilpropil)-2H-tetrazol-5-il]}amino-2-etil-6-triflourometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) fue disuelto en una mezcla de etanol (3 ml) y agua destilada (0,5 ml), y a los mismos fueron agregados monohidrato de hidróxido de litio (34,7 mg) bajo enfriamiento con hielo. La mezcla fue agitada a temperatura ambiente durante 4 días, y a los mismos fueron agregados una solución acuosa saturada de ácido cítrico, y la mezcla fue extraída con cloruro del metileno. La capa orgánica fue lavada con una solución salina saturada, secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo =2:1→1:2) para obtener etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(2-carboxi-2-metilpropil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (262 mg). MS (m/z): 709 $[M-H]^-$

Ejemplos 47-49

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 46 para dar los compuestos enumerados en la Tabla 6.

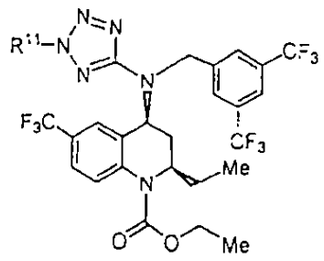
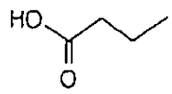
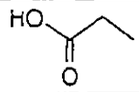
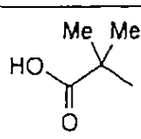


Tabla 6

Ejemplo	R11	Propiedades físicas, etc.
47		MS (m/z):683 [M+H]+
48		MS (m/z):669 [M+H]+
49		MS (m/z):697 [M+H]-

Ejemplo 50

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(3-metiltiopropil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (175 mg) fue disuelto en cloroformo (2 ml), y a los mismos fue agregado ácido m-cloroperbenzoico (422,8 mg), y la mezcla fue agitada a temperatura ambiente durante 30 minutos. A la mezcla fue agregada una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extraída con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel

de sílice; hexano:acetato de etilo = 7:3→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(3-metansulfonilpropil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (180 mg). MS (m/z): 731 $[M+H]^+$

Ejemplo 51

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2-metiltioetil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en cloroformo (2 ml), y fue agregado a los mismos ácido m-cloroperbenzoico (100,1 mg), y la mezcla fue agitada a temperatura ambiente durante 2,5 horas. A la mezcla fue agregado una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extraída con cloruro del metileno. La capa orgánica fue lavada con una solución salina saturada, secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; cloroformo:metanol = 49:1→19:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(2-metansulfoniletil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (9[illegible],9 mg, MS (m/z): 701 $[M+H]^+$) y etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(2-metansulfoniletil)-2H-

tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (118,6 mg, MS (m/z): 717 $[M+H]^+$).

Ejemplo 52

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2,2-dimetil-[1,3]dioxolano-4-ilmetil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (260 mg) fue disuelto en etanol (2 ml), y a los mismos fueron agregados Dowex[tipo H^+] (fabricado por "Dow Chemical Company") (4 g), y la mezcla fue agitada a temperatura ambiente durante 39,5 horas. La mezcla fue filtrada por uso de metanol, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo - 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(2,3-dihidroxipropil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg). MS (m/z): 685 $[M+H]^+$

Ejemplo 53

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(2-oxolanilmetil-2H-tetrazol-5-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) fue disuelto en una solución que fue preparada previamente agregando hidruro de sodio (62,7%, 0,6 mg) en etanol (2 ml), y fue agitada a temperatura ambiente

durante 5 minutos, y la mezcla fue agitada durante 18 horas y 40 minutos. Fue agregado a los mismos agua destilada, y la mezcla fue extractada con éter. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→3:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(3-etoxi-2-hidroxipropil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (92,7 mg). MS (m/z): 713 $[M+H]^+$

Ejemplo 54

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(2-oxolanilmetil-2H-tetrazol-5-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (120 mg) fue disuelto en etanol (1 ml), y a los mismos fueron agregados una solución acuosa de amoníaco al 28% (1 ml). La mezcla fue agitada a temperatura ambiente durante 18,5 horas. La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna (gel de sílice; cloroformo:metanol = 49:1→19:1) para dar etil éster de ácido (2R,4S)-4-{[2-(3-amino-2-hidroxipropil)-2H-tetrazol-5-il]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-

trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (51,2 mg). MS (m/z): 684 $[M+H]^+$

Ejemplos 55-58

Los compuestos de comienzo correspondientes fueron tratados de manera similar al del Ejemplo 54 para dar los compuestos enumerados en la Tabla 7.

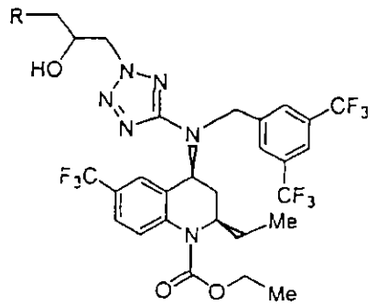
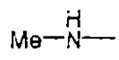
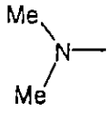
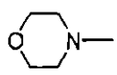
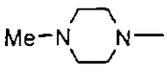


Tabla 7

Ejemplo	R	Propiedades físicas, etc.
55		MS (m/z): 698 $[M+H]^+$
56		MS (m/z): 712 $[M+H]^+$
57		MS (m/z): 754 $[M+H]^+$
58		MS (m/z): 767 $[M+H]^+$

Ejemplo 59

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis-(trifluorometil)bencil]ciano}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (15 g) fue disuelto en

etanol (150 ml), y fueron agregados a los mismos hidrocloruro de hidroxilamina (2,1 g) y trietilamina (4,2 ml), y la mezcla fue agitada a temperatura ambiente durante 18 horas. Fue agregada agua destilada a la mezcla, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 19:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[amino(hidroximino)metil]-[3,5-bis(trifluorometil)benzil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (5,02 g). MS (m/z): 601 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[amino(hidroximino)metil]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (60 mg) fue disuelto en cloruro de metileno (1 ml) y fueron agregados a los mismos diisopropiletilamina (35 µl) y cloruro de ácido hexanoico (18 µl), y la mezcla fue agitada durante 16 horas. Fue agregada agua destilada a la mezcla, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo

resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 19:1→9:1) para dar etil éster de ácido (2R,4S)-4-{[(amino{[(1-oxohexil)oxi]imino}metil)-[3,5-bis(trifluorometil)bencil]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (60,6 mg). MS (m/z): 699 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[(amino{[(1-oxohexil)oxi]imino}metil]-[3,5-bis(trifluoro-metil)bencil]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (37 mg) fue disuelto en etanol (1 ml), y a los mismos fueron agregados metóxido de sodio (0,3 mg), y la mezcla fue agitada durante una hora. Fue agregada agua destilada a la mezcla, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-pentil-[1,2,4]oxadiazolo-3-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (60,6 mg). MS (m/z): 681 $[M+H]^+$

Ejemplo 60

Etil éster de ácido (2R,4S)-4-{[Amino(hidroximino)metil]-[3,5-bis(trifluorometil)-

bencil]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (154 mg) fue disuelto en cloruro de metileno (1,5 ml), y fueron agregados diisopropiletilamina (89 µl) y cloruro de ácido metoxiacetico (30 µl), y la mezcla fue agitada durante 18 horas. Fue agregada agua destilada a la mezcla, y fue extraída con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 2:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-metoximetil-[1,2,4]oxadiazol-3-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (118,3 mg). MS (m/z): 655 $[M+H]^+$

Ejemplos 61-63

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 60 para dar los compuestos enumerados en la Tabla 8.

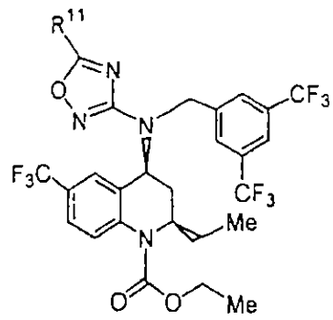
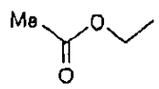
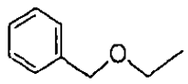
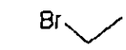


Tabla 8

Ejemplo	R^{11}	Propiedades físicas, etc.
61		MS (m/z): 683 $[M+H]^+$
62		MS (m/z): 731 $[M+H]^+$
63		MS (m/z): 703/705 $[M+H]^+$

Ejemplo 64

Etil éster de ácido (2R,4S)-4-{(5-Acetoximetil-[1,2,4]oxadiazol-3-il)-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (30 mg) fue disuelto en etanol (1 ml), y a los mismos fue agregado carbonato de potasio (60,8 mg), y la mezcla fue agitada durante 30 minutos. Fue agregada agua destilada, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroximetil-[1,2,4]oxadiazol-3-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (22 mg). MS (m/z): 641 $[M+H]^+$

Ejemplo 65

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromometil-[1,2,4]oxadiazol-3-

il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina-1-carboxílico (100 mg) fue disuelto en una mezcla de metanol (0,5 ml) y tetrahidrofurano (0,5 ml), y a los mismos fue agregado morfolina (0,1 ml). La mezcla fue agitada a 45°C durante 2 horas. La mezcla fue enfriada a la temperatura ambiente, y a los mismos fue agregado 1N de ácido clorhídrico, y la mezcla fue extractada con éter. La capa orgánica capa fue lavada con solución salina saturada, fue secada sobre sulfato de magnesio, y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4.1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)metil-[1,2,4]oxadiazol-3-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (69 mg). MS(m/z): 710 $[M+H]^+$

Ejemplos 66-67

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a los del Ejemplo 65 para dar los compuestos enumerados en la Tabla 9.

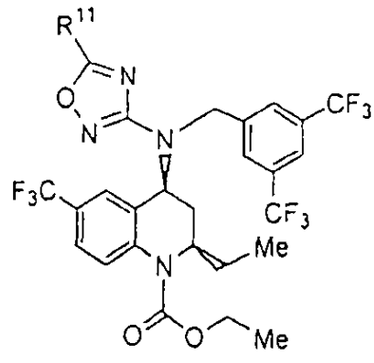
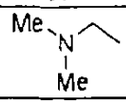
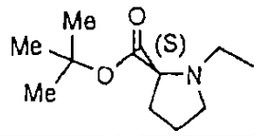


Tabla 9

Ejemplo	R^{11}	Propiedades físicas, etc
66		MS (m/z): 668 $[M+H]^+$
67		MS (m/z): 794 $[M+H]^+$

Ejemplo 68

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-{[5-((2S)-2-terc-butoxicarbonilpirolidin-1-il)metil]-[1,2,4]oxadiazol-3-il}}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (55 mg) fue disuelto en una solución 4N de ácido clorhídrico 1,4-dioxano (0,5 ml), y la mezcla fue agitada toda la noche a temperatura ambiente. La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→cloroformo) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis-(trifluorometil)bencil]-[[5-((2S)-2-carboxipirolidin-1-il)metil]-[1,2,4]-oxadiazol-3-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (27,5 mg). MS (m/z): 738 $[M+H]^+$

Ejemplo 69

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1 g), 4,6-dicloropirimidina (1,9 g), y disopropilamina (824 mg)

fueron disueltos en N,N-dimetilformamida (15 ml), y la mezcla fue agitada a 80°C durante 3 horas. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 19:1→7:3) para dar etil éster de ácido (2R,4S)-4-(6-cloropirimidin-4-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,088 g). MS (m/z): 429/431 [M+H].

(2) Etil éster de ácido (2R,4S)-4-(6-Cloropirimicin-4-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg), bromuro de 3,5-bis(trifluorometil)bencilo (143 mg), y hidruro de sodio (62,7%, 18 mg) fue disuelto en N,N-dimetilformamida (2 ml), y la mezcla fue agitada a 55°C durante 15 minutos. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos una solución acuosa de ácido cítrico y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano: acetato de etilo = 49:1→3:1) para dar etil

éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(6-cloropirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (75 mg). MS (m/z): 655/657 $[M+H]^+$

(3) Una mezcla de etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(6-cloropirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (220 mg) y morfolina (4 ml) fue agitada a 70°C durante 20 minutos. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 19:1→3:2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[6-(morfolin-4-il)pirimidin-4-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (110 mg). MS (m/z): 706 $[M+H]^+$

Ejemplos 70-75

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 69-(3) para dar los compuestos enumerados en la Tabla 10.

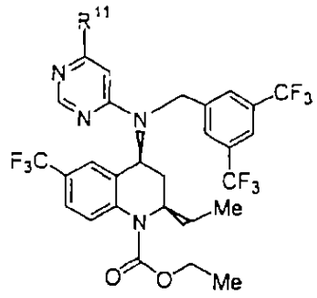
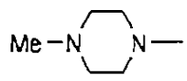
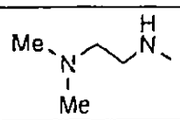
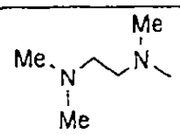
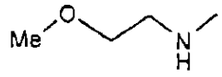
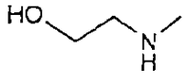
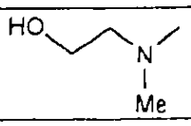


Tabla 10

Ejemplo	R^{11}	Propiedades físicas, etc.
70		MS (m/z): 719 $[M+H]^+$
71		MS (m/z): 707 $[M+H]^+$
72		MS (m/z): 721 $[M+H]^+$
73		MS (m/z): 708 $[M+H]^+$
74		MS (m/z): 680 $[M+H]^+$
75		MS (m/z): 694 $[M+H]^+$

Ejemplo 76

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1 g), 4-cloro-2-metiltiopirimidina (2,04 g), y diisopropiletilamina (890 µl) fueron disueltos en N,N-dimetilformamida (15 ml), y la mezcla fue agitada toda la noche a 100 °C. La solución de reacción fue enfriada a temperatura ambiente, y a los mismos fue agregado una solución acuosa de ácido cítrico y acetato

de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→3:2) para dar etil éster de ácido (2R,4S)-2-etil-4-(2-metiltiopirimidin-4-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,07 g). MS (m/z): 441 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-2-etil-4-(2-metiltiopirimidin-4-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,05 g) y bromuro de 3,5-bis(trifluorometil)bencilo (1,465 g) fue disuelto en N,N-dimetilformamida (10 ml), y a los mismos fue agregado hidruro de sodio (62,7%; 137 mg) a temperatura ambiente, y la mezcla fue agitada durante una hora. A la solución de reacción fue agregado ácido acético, y a los mismos fue agregado agua y éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(2-metiltiopirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,35 g). MS (m/z): 667

$[M+H]^+$

Ejemplo 77

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(2-metiltiopirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (133,2 mg) fue disuelto en cloroformo (3 ml), y a los mismos fue agregado ácido de m-cloroperbenzoico (64,5 mg) a temperatura ambiente, y la mezcla fue agitada durante 5 minutos. A la solución de reacción fue agregado NH-gel de sílice, y el NH-gel de sílice fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano: acetato de etilo = 4:1→0:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(2-metilsulfinilpirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (53 mg, MS (m/z): 683 $[M+H]^+$) y etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(2-metilsulfonilpirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (66 mg, MS (m/z): 699 $[M+H]^+$).

Ejemplo 78

Hidrocloruro de hidroxilamina (269 mg) fue suspendido en dimetilsulfóxido (3 ml), y a los mismos fue agregado trietilamina (0,54 ml). Los materiales insolubles fueron recolectados por filtración, y fueron lavados con

tetrahidrofurano. El tetrahidrofurano fue removido del filtrado por evaporación bajo presión reducida para dar una solución de hidroxilamina en dimetilsulfóxido. A esta solución fue agregado etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-cianopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg), y la mezcla fue agitada a 75°C durante 30 minutos. La mezcla fue enfriada a temperatura ambiente, y a la solución de reacción fueron agregados acetato de etilo y una solución salina saturada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(N-hidroxicarbamimidoil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (520 mg). MS (m/z): 679 $[M+H]^+$

Ejemplo 79

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(2-metilsulfonilpirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) y una cantidad en exceso de 2-aminoetanol fueron disueltos en 1,3-dimetilimidazolidinona (2 ml), y la mezcla fue agitada a 90°C durante una hora. La solución de reacción fue enfriada a temperatura ambiente, y

fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo =3:2→1:4) para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-[2-(2-hidroxietilamino)pirimidin-4-il])amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (72 mg). MS (m/z): 680 $[M+H]^+$

Ejemplos 80-82

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 79 para dar los compuestos enumerados en la Tabla 11.

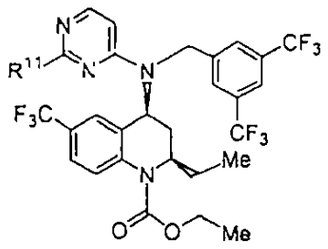
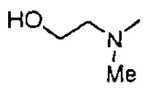
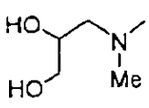
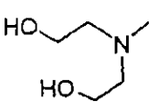


Tabla 11

Ejemplo	R^{11}	Propiedades físicas, etc.
80		MS (m/z): 694 $[M+H]^+$
81		MS (m/z): 724 $[M+H]^+$
82		MS (m/z): 724 $[M+H]^+$

Ejemplo 83

Alcohol 4-Metoxibencílico (136 mg) fue disuelto en N,N-dimetilformamida (3 ml), y a los mismos fueron agregados hidruro de sodio (62,7%, 42 mg) a la temperatura ambiente, y la mezcla fue agitada durante 30 minutos. A la mezcla de reacción fue agregado etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(2-metilsulfonilpirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (686 mg), y la mezcla fue agitada durante 5 horas. Fue agregado ácido acético a la solución de reacción, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[2-(4-metoxibenciloxi)pirimidin-4-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (600 mg). MS (m/z): 757 $[M+H]^+$

Ejemplo 84

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(4-metoxibenciloxi)pirimidin-4-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (570 mg) fue disuelto en 1,4-dioxano (4 ml), y a

los mismos fue agregado ácido clorhídrico concentrado (4 ml) a temperatura ambiente. La solución de reacción fue agitada durante 15 minutos, y fue neutralizada con una solución acuosa saturada de carbonato hidrógeno de sodio. Fue agregado acetato de etilo a la solución de reacción, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 1:1→0:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(2-hidroxipirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (410 mg). MS (m/z): 637 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(2-hidroxipirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (376 mg), 2-iodoetanol (305 mg), y carbonato de cesio (1,152 g) fueron disueltos en N,N-dimetilformamida (5 ml), y la mezcla fue agitada a 60°C durante 3 horas. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de

etilo = 1:1→0:1), luego por cromatografía en columna (gel de sílice; hexano: acetato de etilo = 3:7→0:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[1-(2-hidroxietil)-2-oxo-1,2-dihidropirimidin-4-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (240 mg, MS (m/z): 681 $[M+H]^+$) y etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[1-[2-(2-hidroxietoxi)etil]-2-oxo-1,2-dihidropirimidin-4-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (7 mg, MS (m/z): 725 $[M+H]^+$).

Ejemplo 86

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (5 g) fue disuelto en tolueno (50 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (293 mg), terc-butóxido de sodio (3,8 g), 2-(di-terc-butilfosfino)bifenilo (376 mg), y 2,6-dicloropirazina (4,7 g). La mezcla fue agitada a temperatura ambiente bajo atmósfera de nitrógeno durante 23 horas. A la mezcla fue agregada una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel

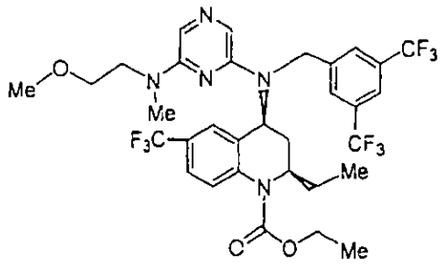
de sílice; hexano:acetato de etilo = 6:1→3:1) para dar etil éster de ácido (2R,4S)-4-(6-cloropirazin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (5,3 g). MS (m/z): 429 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-(6-Cloropirazin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3 g) fue disuelto en N,N-dimetilformamida (35 ml), y fueron agregados a los mismos hidruro de sodio (62,7%, 348 mg) y bromuro de 3,5-bis(trifluorometil)bencilo (9 ml), y la mezcla fue agitada a temperatura ambiente durante 48 horas. Fue agregada agua destilada a la mezcla, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(6-cloropirazin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,6 g). MS (m/z): 655 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(6-cloropirazin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en 1,3-dimetilimidazolidinona (2 ml), y fue agregado a los mismos diisopropiletilamina (80 ul), y

morfolina (140 µl). La mezcla fue agitada a 80°C durante 51 horas, y fue enfriada a temperatura ambiente. Una solución acuosa saturada de ácido cítrico fue agregada a la mezcla, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→13:7) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[6-(morfolin-4-il)pirazin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (132,8 mg). MS (m/z): 706 $[M+H]^+$

Ejemplo 87



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 86 para dar el compuesto de Ejemplo 87. MS (m/z): 708 $[M+H]^+$

Ejemplo 88

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) y 2-cloro-5-nitrotiazolo (416 mg) fueron disueltos en N,N-

dimetilformamida (1 ml), y la mezcla fue agitada a 100°C durante 3 horas. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos una solución acuosa de ácida cítrico y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida, el residuo resultante fue purificado por cromatografía en columna (gel de silicio; hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-2-etil-4-(5-nitrotiazol-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (148 mg). MS (m/z): 445 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-2-etil-4-(5-nitrotiazol-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (133 mg) y bromuro de 3,5-bis(trifluorometil)bencilo (179 mg) fueron disueltos en tetrahidrofurano (3 ml), y a los mismos fue agregado hidruro de sodio (62,7%; 34 mg), y la mezcla fue agitada a temperatura ambiente toda la noche. A la solución de reacción fue agregado ácido acético, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→2:1) para dar etil

éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-nitrotiazol-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (58 mg). MS (m/z): 671 $[M+H]^+$

Ejemplo 89

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-ciano}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (327,9 mg) fue disuelto en tetrahidrofurano (3 ml), y a los mismos fue agregado hidruro de sodio (62,7%; 13,9 mg). La mezcla fue agitada con enfriamiento con hielo dentro de una atmósfera nitrógeno durante una hora. A la solución de reacción fue agregado en forma lenta una solución de 3-buten-1-ol (41,8 mg) en tetrahidrofurano (4 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a temperatura ambiente durante 29 horas. Fue agregada agua destilada bajo enfriamiento con hielo, y la mezcla fue extraída con acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo 4:1) para dar etil éster de ácido (2R,4S)-4-{1-[3,5-bis(trifluorometil)bencil]-2-(3-buten-1-il)}isoureido-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (186,3 mg). MS (m/z): 640 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{1-[3,5-Bis(trifluorometil)bencil]-2-(3-buten-1-il)}isoureido-2-etil-

6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (172 mg) fue disuelto en cloroformo (3 ml), y a los mismos fueron agregados N-iodosuccimida (72,5 mg). La mezcla fue agitada a temperatura ambiente durante 1,5 horas, y a los mismos fue agregada una solución acuosa saturada de tiosulfato de sodio. La mezcla fue extraída con éter, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida para dar etil éster de ácido (2R,4S)-4-{[3,5bis(trifluorometil)bencil]-(4-iodometil-5,6-dihidro-4H-[1,3]oxadin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (211 mg). MS (m/z): 766 $[M+H]^+$

Ejemplo 90

(1) Etil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) fue disuelto en N,N-dimetilformamida (1 ml), y a los mismos fue agregado hidruro de sodio (62,7%; 10,3 mg), y la mezcla fue agitada con enfriamiento cor hielo dentro de una atmósfera de nitrógeno durante 10 minutos. bromuro de 3,5-dimetoxibencilo (74 mg) fue agregado a la mezcla bajo enfriamiento con hielo, y la mezcla fue agitada a temperatura ambiente durante 16,5 horas. Fue agregada agua destilada a la mezcla bajo enfriamiento con hielo, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de

magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-[(5-bromopirimidin-2-il)-(3,5-dimetoxibencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (95,1 mg). MS (m/z): 623/625 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[(5-Bromopirimidin-2-il)-(3,5-dimetoxibencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (290 mg) fue disuelto en tolueno (4 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (8,5 mg), terc-butóxido de sodio (68,2 mg), 2-(di-tertbutilfosfina)bifenilo (11 mg) y morfolina (62 µl). La mezcla de reacción fue agitada dentro de una atmósfera de nitrógeno a temperatura ambiente durante 4 días. La solución de reacción fue agitada a 80°C durante 5,5 horas, y fue enfriada hasta la temperatura ambiente. Fue agregada agua destilada a la mezcla, y la mezcla fue extractada con éter. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{(3,5-dimetoxibencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-

3,4-dihidro-2H-quinolin-1-carboxílico (141,5 mg). MS (m/z): 630 $[M+H]^+$

Ejemplos 91-94

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 90 para dar los compuestos enumerados en la Tabla 12.

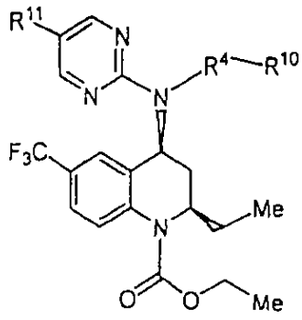
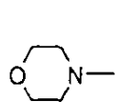
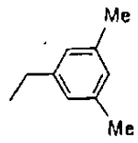
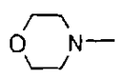
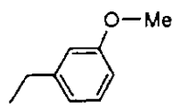
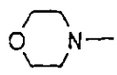
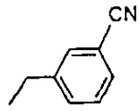
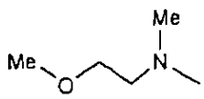
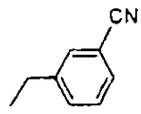


Tabla 12

Ejemplo	R^{11}	R^4-R^{10}	Propiedades físicas, etc.
91			MS (m/z): 598 $[M+H]^+$
92			MS (m/z): 600 $[M+H]^+$
93			MS (m/z): 595 $[M+H]^+$
94			MS (m/z): 597 $[M+H]^+$

Ejemplo 95

(1) 6-Bromopiridin-2-carbaldeido (5 g) fue disuelto en una mezcla de metanol (10 ml) y tetrahidrofurano (15 ml), y a

los mismos fue agregado borohidruro de sodio (3,05 g) a 0°C, y la mezcla fue agitada durante 10 minutos. A la solución de reacción fue agregada una solución acuosa de ácido cítrico y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano: acetato de etilo = 9:1→2:3) para dar (6-bromopiridin-2-il)metanol (3,92 g). MS (m/z): 188 / 190 $[M+H]^+$

(2) (6-Bromopiridin-2-il)metanol (3,9 g) y trifenilfosfina (7,6 g) fueron disueltos en cloruro de metileno (50 ml), y a los mismos fue agregado tetrabromuro de carbono (8,25 g) bajo enfriamiento con hielo. La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 49:1→47:3) para dar 2-bromo-6-bromometilpiridina (2,96 g). MS (m/z): 250/252 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolir-1-carboxílico (400 mg) fue disuelto en N,N-dimetilformamida (4 ml), y a los mismos fue agregado a 10°C hidruro de sodio (62,7%; 42 mg). La mezcla fue agitada a la misma temperatura durante 10 minutos, y a la solución de reacción fue agregado 2-bromo-6-bromometilpiridina (318 mg). La mezcla fue agitada

a la misma temperatura durante 15 minutos, y a los mismos fue agregado ácido acético. A la mezcla fueron agregados una mezcla de solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 48:2→3:2) para dar etil éster de ácido (2R,4S)-4-[(6-bromopiridin-2-il)metil-(5-bromopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (470 mg). MS (m/z): 642 / 644 $[M+H]^+$

(4) Etil éster de ácido (2R,4S)-4-[(6-bromopiridin-2-il)metil-(5-bromopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (150 mg), tetrakis(trifenilfosfina)paladio (28 mg) y cianuro de zinc (71,2 mg) fueron disueltos en N,N-dimetilformamida (3 ml), y la mezcla fue agitada toda la noche a 95°C dentro de una atmósfera de nitrógeno. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 47:3→2:3)

para dar etil éster de ácido (2R,4S)-4-[(6-cianopiridin-2-il)metil-(5-cianopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (105 mg). MS (m/z): 536 $[M+H]^+$

Ejemplos 96-97

Etil éster de ácido (2R*,4S*)-4-amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico fue tratado de una manera similar a la del Ejemplo 1 para dar los compuestos enumerados en la Tabla 13.

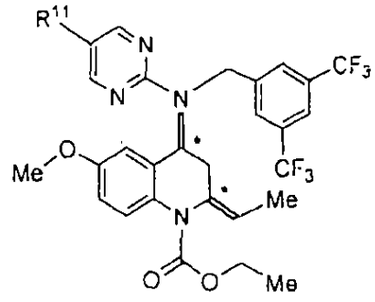
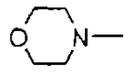
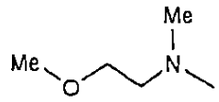
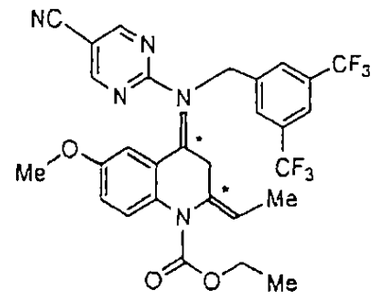


Tabla 13

Ejemplo	Configuración	R^{11}	Propiedades físicas, etc.
96	(2R*,4S*)		MS (m/z): 668 $[M+H]^+$
97	(2R*,4S*)		MS (m/z): 670 $[M+H]^+$

Ejemplo 98



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 10 para dar los compuestos del Ejemplo 98. MS (m/z): 608 $[M+H]^+$

Ejemplo 99

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (284 mg), bencil éster de ácido acrílico (125 mg), tris(dibencilidenacetona)dipaladio (292 mg), diciclohexilmetilamina (110 µl), y tetrafluoroborato de tri(terc-butil)fosfonio (308 mg) fue disuelto en 1,4-dioxano (4 ml), y la mezcla fue agitada a temperatura ambiente dentro de una atmósfera de nitrógeno toda la noche. La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R*,4S*)-4-{[5-(2-benciloxi-carbonilvinil)pirimidin-2-il]-[3,5-bis(trifluoro-metil)bencil]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (266 mg). MS (m/z): 743 $[M+H]^+$

Ejemplo 100

Etil éster de ácido (2R*,4S*)-4-{[5-(2-Benciloxicarbonilvinil)pirimidin-2-il]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-metoxi-3,4-dihidro-

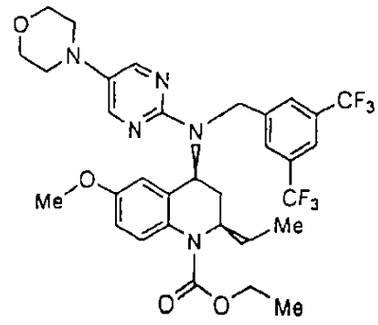
2H-quinolin-1-carboxílico (265 mg) fue disuelto en una mezcla de metanol (4 ml) y tetrahidrofurano (1 ml), y a los mismos fue agregado una cantidad catalítica de 10% paladio-carbono, y la mezcla fue agitada a temperatura ambiente dentro de una atmósfera de hidrógeno durante 3 horas. El catalizador (10% paladio-carbono) fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-carboxivinil)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (176 mg). MS (m/z): 653 $[M+H]^+$

Ejemplo 101

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-carboxivinil)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (120 mg) fue disuelto en una mezcla de metanol (4 ml) y tetrahidrofurano (1 ml), y una cantidad catalítica de 10% paladio-carbono fue agregada a los mismos, y la mezcla fue agitada a temperatura ambiente dentro de una atmósfera de hidrógeno toda la noche. El catalizador fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de

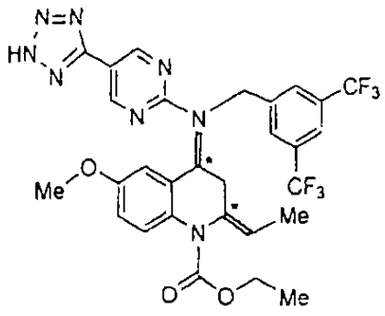
etilo = 4:1) para dar etil éster de ácido (2R*,4S*)-4-([3,5-bis(trifluorometil)bencil]-[5-(2-carboxietil)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (35 mg). MS (m/z): 655 $[M+H]^+$

Ejemplo 102



Etil éster de ácido (2R,4S)-4-amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico fue tratado de una manera similar a la del Ejemplo 1 para dar el compuesto del Ejemplo 102. MS (m/z): 668 $[M+H]^+$

Ejemplo 103



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 19 para dar el compuesto del Ejemplo 103. MS (m/z): 651 $[M+H]^+$

Ejemplos 104-105

Los compuestos de comienzo correspondientes fueron

tratados en una manera similar a la del Ejemplo 20 para dar los compuestos enumerados en la Tabla 14.

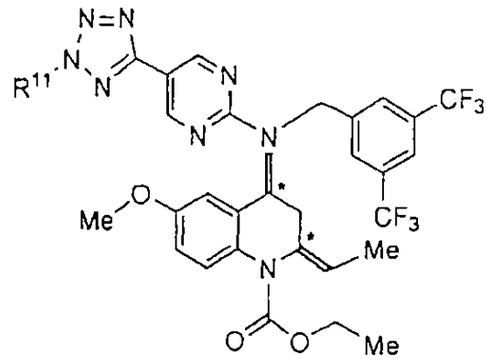
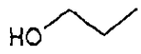


Tabla 14

Ejemplo	Configuración	R^{11}	Propiedades físicas, etc.
104	(2R*,4S*)	CH_3-	MS (m/z): 665 $[M+H]^+$
105	(2R*,4S*)		MS (m/z): 695 $[M+H]^+$

Ejemplos 106-109

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 35 para dar los compuestos enumerados en la Tabla 15.

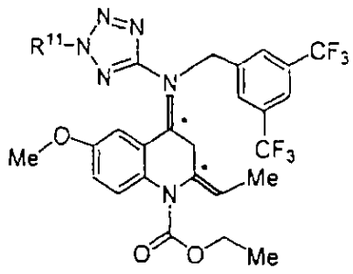
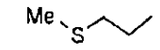
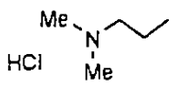
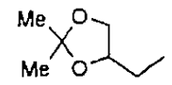
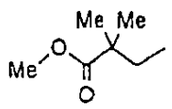


Tabla 15

Ejemplo	Configuración	R^{11}	Propiedades físicas, etc.
106	(2R*,4S*)		MS (m/z): 647 $[M+H]^+$
107	(2R*,4S*)		MS (m/z): 644 $[M+H]^+$
108	(2R*,4S*)		MS (m/z): 687 $[M+H]^+$
109	(2R*,4S*)		MS (m/z): 687 $[M+H]^+$

Ejemplo 110

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2-metiltioetil)2H-tetrazol-5-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (226 mg) fue disuelto en cloruro de metileno (3 ml), y a los mismos fue agregado ácido m-cloroperbenzoico (75 mg) a temperatura ambiente, y la mezcla fue agitada toda la noche. A la solución de reacción fue agregado una solución acuosa de carbonato de potasio, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; cloroformo:metanol = 1:0→20:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[2-(2-metilsulfinil-etil)2H-tetrazol-5-il]}amino-2-etil-6-metoxi-

3,4-dihidro-2H-quinolin-1-carboxílico (176 mg). MS (m/z): 663 $[M+H]^+$

Ejemplo 111

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2-metilsulfiniletil)-2H-tetrazol-5-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (117 mg) fue disuelto en cloruro de metileno (2 ml), y a los mismos fue agregado ácido m-cloroperbenzoico (76 mg) a temperatura ambiente. La mezcla fue agitada toda la noche, y a la solución de reacción fue agregada una solución acuosa de carbonato de potasio. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 2:1→1:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[2-(2-metilsulfoniletil)-2H-tetrazol-5-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (108 mg). MS (m/z): 679 $[M+H]^+$

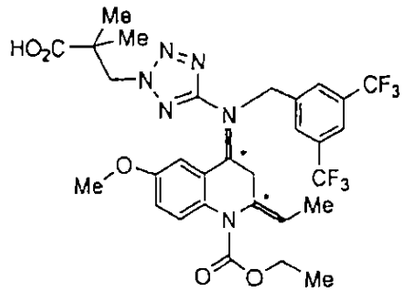
Ejemplo 112

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2,2-dimetil-[1,3]dioxolan-4-ilmetil)-2H-tetrazol-5-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (129 mg) fue disuelto en una mezcla de metanol (3 ml) y agua (0,3 ml), y fueron agregados a los

mismos a temperatura ambiente una resina fuertemente ácida (IR-120, fabricada por "Organo Corporation") (50 mg) y ácido clorhídrico 6N (2 ml), y la mezcla fue agitada toda la noche. La resina fue eliminada por filtración, y al filtrado fueron agregados una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-{2-(2,3-dihidroxipropil)-2H-tetrazol-5-il}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (123 mg). MS (m/z): 647 $[M+H]^+$

Ejemplo 113

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 46 para dar el compuesto de la fórmula siguiente. MS (m/z): 673 $[M+H]^+$



Ejemplos 114-115

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 60 para dar los compuestos enumerados en la Tabla 16.

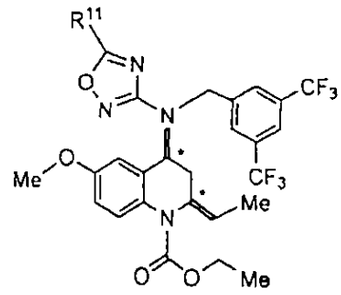
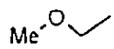
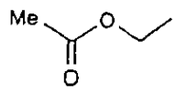
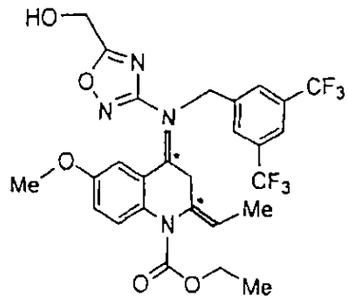


Tabla 16

Ejemplo	Configuración	R^{11}	Propiedades físicas, etc.
114	(2R*,4S*)		MS (m/z): 634 $[M+H_2O]^+$
115	(2R*,4S*)		MS (m/z): 662 $[M+H_2O]^+$

Ejemplo 116

Los compuestos de comienzo correspondientes fueron tratan de una manera similar a la del Ejemplo 64 para dar el compuesto de la fórmula siguiente. MS (m/z): 620 $[M+H_2O]^+$



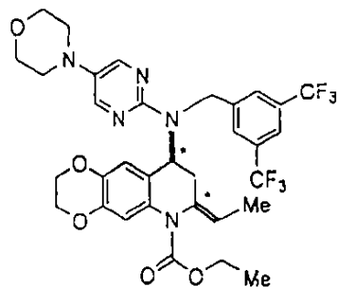
Ejemplo 117

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-bromopirimidin-2-il]}amino-6-bromo-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (1,48 g), tris(dibencilidenacetona)dipaladio (190 mg), trec-butoxido de

sodio (401 mg), 2-(di-terc-butilfosfino)bifenilo (124 mg), y morfolina (197 ul) fueron disueltos en tolueno (15 ml), y la mezcla fue agitada dentro de una atmósfera de nitrógeno a temperatura ambiente durante 96 horas. A la solución de reacción fueron agregados solución salina saturada y acetato de etilo, y la capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo =9:1→67:33) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluoro-metil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-(morfolin-4-il)-3,4-dihidro-2H-quinolin-1-carboxílico (320 mg, MS (m/z): 723 $[M+H]^+$) y etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-6-bromo-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (568 mg, MS (m/z): 716/718 $[M+H]^+$).

Ejemplo 118

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 1 para dar el compuesto de la fórmula siguiente. MS (m/z): 696 $[M+H]^+$



Ejemplo 119

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(N-hidroxicarbamimidoil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) y 1,1'-carbonilimidazol (72 mg) fueron disueltos en acetonitrilo (5 ml), y la mezcla fue agitada durante 2 horas. La mezcla fue enfriada a temperatura ambiente, y a la solución de reacción fueron agregados acetato de etilo y solución acuosa saturada de carbonato hidrógeno de sodio. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(5-oxo-4,5-dihidro-[1,2,4]-oxadiazol-3-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (60 mg). MS (m/z): 705 $[M+H]^+$

Ejemplo 120

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,83 g), yoduro de cobre (I) (150 mg), yoduro de sodio (2,36 g), y N,N'-dimetiletilendiamina (168 µl) fueron disueltos en

1,4-dioxano (8 ml), y la mezcla fue agitada a 105°C dentro de una atmósfera de nitrógeno durante 23 horas. La solución de reacción fue enfriada hasta la temperatura ambiente, y a los mismos fueron agregados agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→6:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-iodopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,70 g). MS (m/z): 747 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-iodopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,69 g), 3-metoxi-3-oxopropano-1-sulfinato de sodio (1,58 g), y yoduro de cobre(I) (1,72 g) fueron disueltos en dimetilsulfóxido (20 ml), y la mezcla fue agitada a 110°C dentro de una atmósfera de nitrógeno durante 2,5 horas. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. Los materiales insolubles precipitados fueron eliminados por filtración a través de "Celite^{MR}", y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida.

El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→2:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-metoxicarboniletansulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,41 g). MS (m/z): 771 $[M+H]^+$

Ejemplos 121-123

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 1-(3) para dar los compuestos enumerados en la Tabla 17.

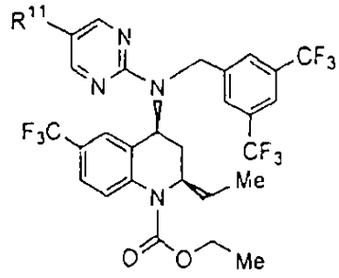
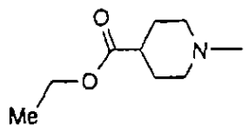
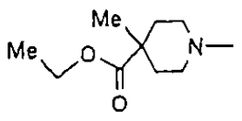
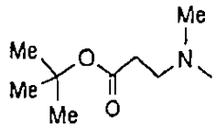


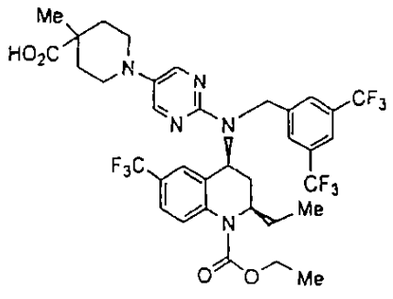
Tabla 17

Ejemplo	R^{11}	Propiedades físicas, etc.
121		MS (m/z): 776 $[M+H]^+$
122		MS (m/z): 790 $[M+H]^+$
123		MS (m/z): 778 $[M+H]^+$

Ejemplo 124

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (265 mg) fue disuelto en etanol (3 ml), y a los mismos fue agregado una solución acuosa de hidróxido de sodio 2N (0,342 ml), y la mezcla fue agitada a 50°C durante una hora. La mezcla fue enfriada a temperatura ambiente, y la solución de reacción fue acidificada con ácido clorhídrico 1N. La mezcla fue extraida con acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol =1:0→9:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (241 mg). MS (m/z): 748 $[M+H]^+$

Ejemplo 125.

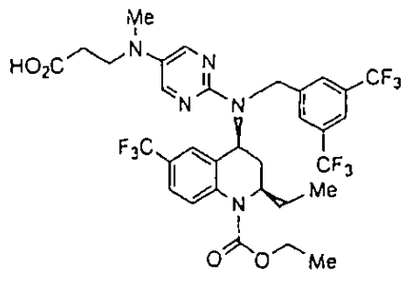


Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 124 para dar el compuesto del Ejemplo 125. MS (m/z): 762 $[M+H]^+$

Ejemplo 126

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)-bencil]-[5-(2-metoxicarbonil-etansulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (700 mg) y solución 2N acuosa de hidróxido de sodio (1,8 ml) fueron disueltos en etanol (10 ml), y la mezcla fue agitada a 50°C por 30 minutos. La solución de reacción fue enfriada a temperatura ambiente, y fue agregada solución 2N acuosa de ácido clorhídrico (1,8 ml) y acetato de etilo bajo enfriamiento con hielo. La capa orgánica fue lavada con solución salina saturada, secada sobre sulfato de magnesio, y concentrada bajo presión reducida. El residuo resultante se purificó por cromatografía en columna de gel de sílice (cloroformo:metanol = 99:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-sulfopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (384 mg). MS (m/z):699 $[M-H]^-$

Ejemplo 127



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 68 para dar el compuesto del Ejemplo 127. MS (m/z): 722 $[M+H]^+$

Ejemplo 128

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-sulfopirimidin-2-il)}aminc-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (225 mg) fue disuelto en cloruro del tionilo (5 ml), y la mezcla fue agitada a 80°C durante 2 horas. La solución de reacción fue enfriada a temperatura ambiente, y fue concentrada bajo presión reducida. Al residuo resultante fue agregado cloroformo (3 ml), y a los mismos fue agregada una solución 2N de amina de metilo en tetrahidrofurano (3 ml) bajo enfriamiento con hielo. La mezcla fue agitada a temperatura ambiente durante 2 horas, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→2:1) para producir etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil)-(5-metilsulfamoilpirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (68 mg).

MS (m/z): 714 $[M+H]^+$

Ejemplo 129

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-sulfopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (584 mg) fue disuelto en cloruro de tionilo (5 ml), y la mezcla fue agitada a 80°C durante 2 horas. La solución de reacción fue enfriada a temperatura ambiente, y fue concentrada bajo presión reducida. Al residuo resultante fue agregado cloroformo (3 ml), y fue agregada a los mismos una solución 7N de amoníaco en metanol (3 ml) bajo enfriamiento con hielo. La mezcla fue agitada a temperatura ambiente durante 2 horas, y fue agregado a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y luego fue concentrada bajo presión reducida. El residuo resultante entonces fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→2:1) para producir etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-metoxisulfinilpirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (340 mg, MS (m/z): 699 $[M+H]^+$) y etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil](5-sulfamoilpirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (22 mg, MS (m/z): 700 $[M+H]^+$).

Ejemplos 130-133

Los compuestos de comienzo correspondientes fueron tratados de una manera similar al Ejemplo 90 para dar los compuestos enumerados en la Tabla 18.

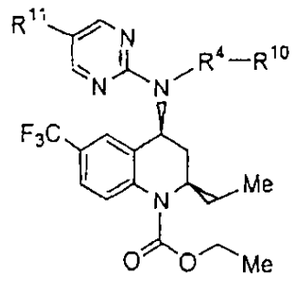
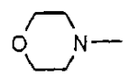
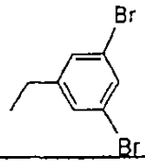
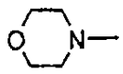
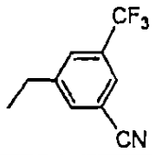
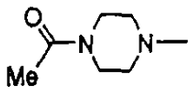
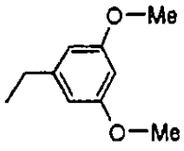
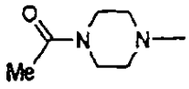
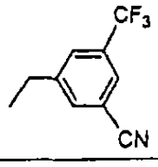


Tabla 18

Ejemplo	R^{11}	R^4-R^{10}	Propiedades físicas, etc.
130			MS (m/z): 726/728/730 $[M+H]^+$
131			MS (m/z): 663 $[M+H]^+$
132			MS (m/z): 671 $[M+H]^+$
133			MS (m/z): 704 $[M+H]^+$

Ejemplo 134

Etil éster de ácido (2R,4S)-4-{(3,5-Dibromobencil)-[(5-morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-

3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en N,N-dimetilformamida (4 ml), y fueron agregados a los mismos cianuro de zinc (71 mg) y una cantidad catalítica de tetrakis(trifenilfosfina)paladio, y la mezcla fue agitada a 110°C dentro de una atmósfera de nitrógeno 2,5 horas. La mezcla fue enfriada a temperatura ambiente, y a los mismos fueron agregados una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extraida con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{(3,5-dicianobencil)-[(5-morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (124 mg). MS (m/z): 620 $[M+H]^+$

Ejemplos 135-136

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 99 para dar los compuestos enumerados en la Tabla 19.

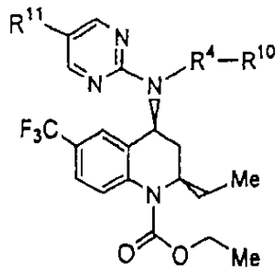
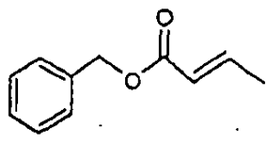
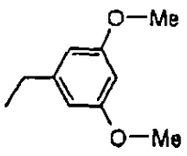
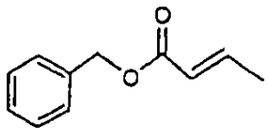
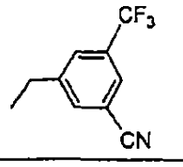


Tabla 19

Ejemplo	R^{11}	R^1-R^{10}	Propiedades físicas. etc.
135			MS (m/z): 705 $[M+H]^+$
136			MS (m/z): 738 $[M+H]^+$

Ejemplo 137

(1) Etil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (18 g) fue disuelto en tetrahidrofurano (180 ml), y a los mismos fueron agregados dicarbonato de di-terc-butilo (12,4 g) y una cantidad catalítica de 4-dimetilaminopiridina, y la mezcla fue agitada a temperatura ambiente toda la noche. A la solución de reacción fue agregada una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extraída con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 8:1) para dar etil éster de ácido (2R,4S)-4-[(terc-butoxicarbonil)-(5-bromopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (22,5 g). MS (m/z): 473/475 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[(terc-butoxicarbonil)-(5-bromopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (5 g) fue disuelto en 1,4-dioxano (60 ml), y fueron agregados a los mismos bencil éster de ácido acrílico (2,83 g), tris(dibencilidenacetona)-dipaladio (1,2 g), tetrafluoroborato de tri(terc-butil)fosforo (760 mg), y N,N diciclohexilmetilamina (1,87 g). La mezcla fue agitada a temperatura ambiente dentro de una atmósfera de nitrógeno durante 2,5 horas, y fue agregada a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio. La mezcla fue extraída con acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-[(terc-butoxicarbonil)-[5(2-benciloxicarbonilvinil)pirimidin-2-il]]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,65 g). MS (m/z): 655 $[M+H]^+$

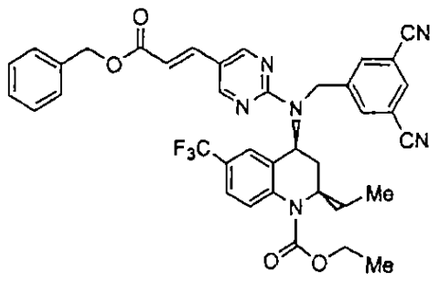
(3) Etil éster de ácido (2R,4S)-4-[(terc-butoxicarbonil)-[5-(2-benciloxicarbonilvinil)pirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,65 g) fue disuelto en cloruro de metileno (10 ml), y a los mismos fueron agregados ácido trifluoracético (1 ml). La mezcla fue

agitada a temperatura ambiente toda la noche, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-[5-(2-benciloxicarbonilvinil)pirimidin-2-il]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,38 g). MS (m/z): 555 $[M+H]^+$

(4) Etil éster de ácido (2R,4S)-4-[5-(2-Benciloxicarbonilvinil)pirimidin-2-il]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,41 g) fue disuelto en N,N-dimetilformamida (30 ml), y a los mismos fueron agregados hidruro de sodio (62,7%; 360 mg) bajo enfriamiento con hielo. La mezcla fue agitada bajo enfriamiento con hielo durante 30 minutos, y a los mismos fueron agregados bromuro de 5-dibromobencil (3 g). La mezcla fue agitada a temperatura ambiente durante una hora. A la solución de reacción fue agregada una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extraida con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por la cromatografía (gel de sílice; hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[5-(2-

benciloxicarbonilvinil)pirimidin-2-il](3,5-dibromobencil)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,84 g). MS (m/z): 801/803/805 $[M+H]^+$

Ejemplo 138



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 134 para dar el compuesto del Ejemplo 138. MS (m/z): 801/803/805 $[M+H]^+$

Ejemplos 139-141

Los compuestos de comienzo correspondientes fueron tratados en una manera similar a la del Ejemplo 18-(2) para dar los compuestos enumerados en la Tabla 20.

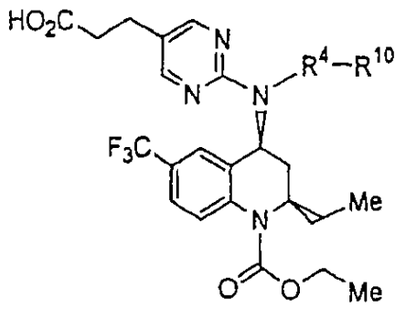
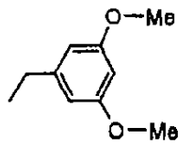
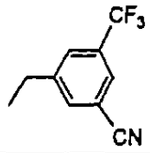
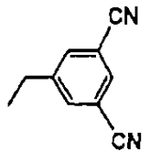


Tabla 20

Ejemplo	R^4-R^{10}	Propiedades físicas, etc.
139		MS (m/z): 617 $[M+H]^+$
140		MS (m/z): 650 $[M+H]^+$
141		MS (m/z): 607 $[M+H]^+$

Ejemplo 142

Etil éster de ácido (2R,4S)-4-{[5-(2-carboxietil)pirimidin-2-il]-(3,5-dimetoxibencil)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (145 mg) y trietilamina (98 µl) fueron disueltos en tetrahidrofurano (3 ml), y a los mismos fue agregado de forma lenta clorocarbonato de etilo (67 µl) a 0°C. La mezcla fue agitada a la misma temperatura durante 30 minutos, y a los mismos fue agregado borohidruro de sodio (44 mg). La mezcla fue agitada a la misma temperatura durante 3 horas. A la solución de reacción fue agregada una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo

presión reducida. El residuo resultante fue purificaco por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-{(3,5-dimetoxibencil)-[5-(3-hidroxipropil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (68 mg). MS (m/z): 603 $[M+H]^+$

Ejemplo 143

Etil éster de ácido (2R,4S)-4-[(3,5-Dimetoxibencil)-(5-iodopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (302 mg) fue disuelto en N,N-dimetilformamida (2,5 ml), y fueron agregados a los mismos tetrakis(trifenilfosfina)paladio (104 mg), ácido pirimidin-5-borónico (112 mg) y carbonato de sodio (111 mg). La mezcla fue agitada a 100°C en una atmósfera de nitrógeno durante 4 horas. La mezcla fue enfriada a temperatura ambiente, y a los mismos fue agregado agua. La mezcla fue extraida con acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 2:1) para producir etil éster de ácido (2R,4S)-4-[([5,5']bipirimidin-2-il)-(3,5-dimetoxibencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (106 mg).

MS (m/z):,623 $[M+H]^+$

Ejemplo 144

(1) Etil éster de ácido (2R,4S)-4-[(3,5-Dimetoxibencil)-(5-iodopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,89 g) fue disuelto en tolueno (12 ml), y fueron agregados a los mismos alcohol bencílico (1,2 ml), yoduro de cobre(I) (221 mg), carbonato de cesio (1,89 g), y 1,10-fenantrolina (418 mg), y la mezcla fue agitada a 100°C durante un día. A la solución de reacción fueron agregados agua y acetato de etilo, y la mezcla fue filtrada a través de Celite^{MR} para eliminar los materiales insolubles. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tolueno (12 ml), y fueron agregados a los mismos alcohol bencílico (0,3 ml), yoduro de cobre(I) (221 mg), carbonato de cesio (1,89 g), y 1,10-fenantrolina (418 mg). La mezcla fue agitada a 100°C durante un día, y fue enfriada a temperatura ambiente. A la solución de reacción fueron agregados agua y éter acético, y la mezcla fue filtrada a través de Celite^{MR} para quitar los materiales insolubles. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4[(3,5-

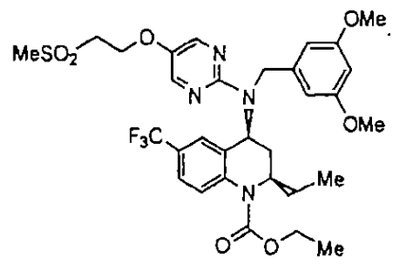
dimetoxibencil)-(5-benciloxipirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,09 g). MS (m/z): 651 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[(3,5-Dimetoxibencil)-(5-benciloxipirimidin-2-il)]amino2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,05 g) fue disuelto en metanol (10 ml), y a los mismos fueron agregados 10% paladio-carbono (1 g). La mezcla fue agitada a temperatura ambiente dentro de una atmósfera de hidrógeno durante una hora. La solución de reacción fue filtrada, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-[(3,5-dimetoxibencil)-(5-hidroxipirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,84 g). MS (m/z): 561 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-[(3,5-Dimetoxibencil)-(5-hidroxipirimidin-2-il)]-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en tetrahidrofurano (2 ml), y fueron agregados a los mismos 2-metilsulfaniletanol (0,05 ml), trifenilfosfina (150 mg), una solución al 40% de azodicarboxilato de dietilo en tolueno (0,25 ml), y la mezcla fue agitada a temperatura ambiente durante 2,5 horas. Fue agregada agua a la mezcla, y la mezcla fue extraída con acetato de etilo. La capa orgánica fue

lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{(3,5-dimetoxibencil)-[5-(2-metilsulfaniletoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (224 mg). MS (m/z): 635 $[M+H]^+$

Ejemplo 145



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 50 para dar el compuesto del Ejemplo 145. MS (m/z): 667 $[M+H]^+$

Ejemplos 146-149

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 96 para dar los compuestos enumerados en la Tabla 21.

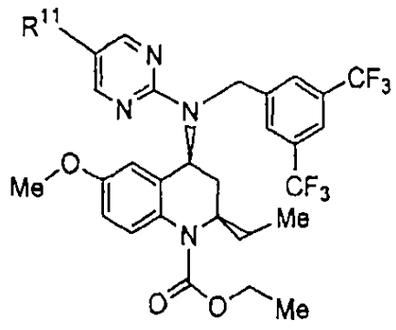
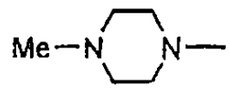
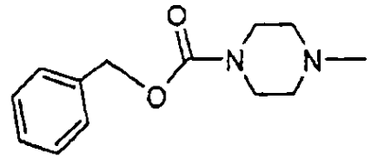
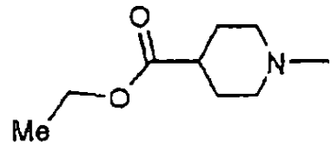
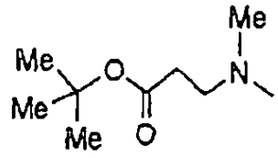


Tabla 21

Ejemplo	R^{11}	Propiedades físicas, etc.
146		MS (m/z): 681 $[M+H]^+$
147		MS (m/z): 801 $[M+H]^+$
148		MS (m/z): 738 $[M+H]^+$
149		MS (m/z): 740 $[M+H]^+$

Ejemplo 150

Etil éster de ácido (2R,4S)-4-{[5-(4-Benciloxicarbonilpiperazin-1-il)pirimidin-2-il]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (1,78 g) fue disuelto en etanol (50 ml), y a los mismos fueron agregados 10% paladio-carbono (300

mg). La mezcla fue agitada a temperatura ambiente dentro de una atmósfera de hidrógeno durante 3 horas. El catalizador (10 % el paladio-carbono) fue separado por filtración, y el filtrado fue concentrado bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(piperazin-1-il)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (470 mg). MS (m/z): 667 $[M+H]^+$

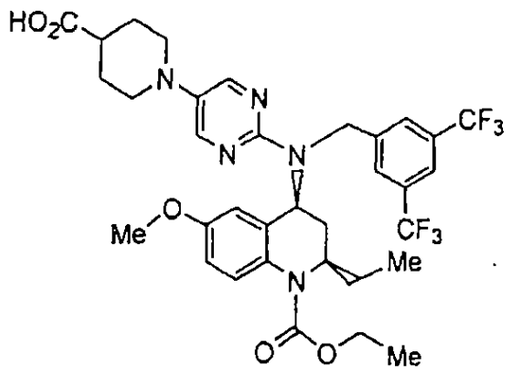
Ejemplo 151

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(piperazin-1-il)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) y piridina (18 µl) fueron disueltos en cloruro de metileno (1 ml), y fue agregado a los mismos cloruro de ácido acetoxiacético (19,4 µl) a temperatura ambiente. La mezcla fue agitada toda la noche, y fue lavada con ácido clorhídrico 1N. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 7:3→2:3) para dar etil éster de ácido (2R,4S)-4-({5-[4-(2-acetoxiacetil)piperazin-1-

il)pirimidin-2-il}-[3,5-bis(trifluorometil)bencil])amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (110 mg). MS (m/z): 767 $[M+H]^+$

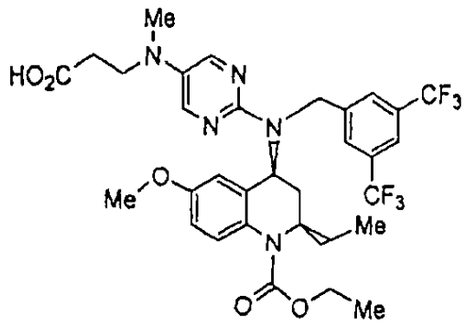
(2) Etil éster de ácido (2R,4S)-4-({5-[4-(2-acetoxiacetil)piperazin-1-il]pirimidin-2-il}-[3,5-bis(trifluorometil)bencil])amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (87 mg) fue disuelto en etanol (1 ml), y a los mismos fue agregado carbonato de potasio (23 mg) a temperatura ambiente, y la mezcla fue agitada toca una noche. Los materiales insolubles fueron eliminados por filtración, y el filtrado fue concentrado bajo presión reducida para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-{5-[4-(2-hidroxiacetil)piperazin-1-il]pirimidin-2-il})amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (83 mg). MS (m/z): 725 $[M+H]^+$

Ejemplo 152



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 124 dar el compuesto del Ejemplo 152. MS (m/z): 710 $[M+H]^+$

Ejemplo 153



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 68 para dar el compuesto del Ejemplo 153. MS (m/z): 684 $[M+H]^+$

Ejemplos 154-156

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 90 para dar los compuestos enumerados en la Tabla 22.

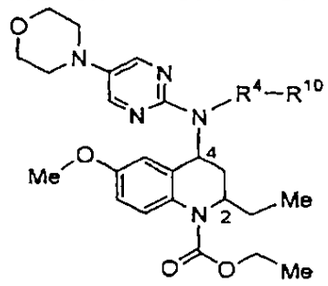
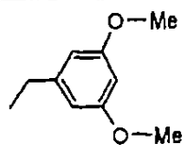
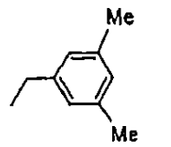
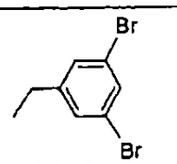
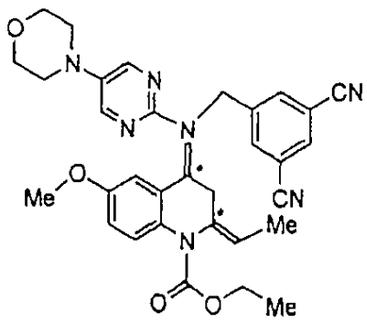


Tabla 22

Ejemplo	Configuración	R^4-R^{10}	Propiedades físicas. etc.
154	(2R,4S)		MS (m/z): 592[$M+H]^+$
155	(2R,4S)		MS (m/z): 560 $[M+H]^+$
156	(2R*,4S*)		MS (m/z): 688/690/692 $[M+H]^+$

Ejemplo 157



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 134 para dar el compuesto del Ejemplo 157. MS (m/z): 582 $[M+H]^+$

Ejemplo 158

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(6-cloropirimidin-4-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg), una cantidad en exceso de trietilamina, y terc-butil éster de ácido aminoacético (501 mg) fueron disueltos en 1,3-dimetilimidazolidinona (4 ml), y la mezcla fue agitada a 90°C durante 3 días. La solución de reacción fue enfriada a temperatura ambiente, y a los mismos fueron agregados una solución acuosa saturada de ácido cítrico y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentraca bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 19:1→13:7) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil)-[6-(terc-butoxicarbonil-

metilamino)pirimidin-4-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (22 mg). MS (m/z): 750 $[M+H]^+$

Ejemplos 159-161

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 158 para dar los compuestos enumerados en la Tabla 23.

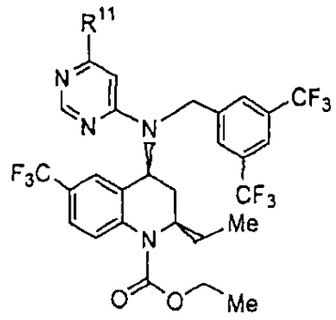
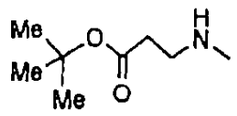
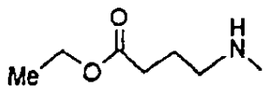
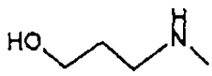


Tabla 23

Ejemplo	R^{11}	Propiedades físicas, etc.
159		MS (m/z): 764 $[M+H]^+$
160		MS (m/z): 750 $[M+H]^+$
161		MS (m/z): 694 $[M+H]^+$

Ejemplo 162-163

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 68 para dar los compuestos enumerados en la Tabla 24.

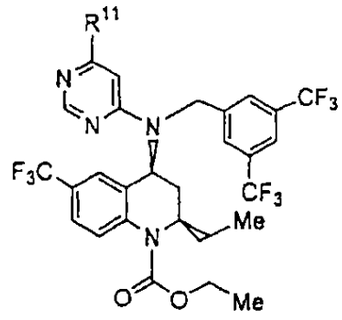
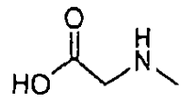
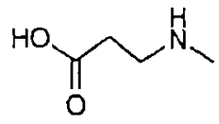
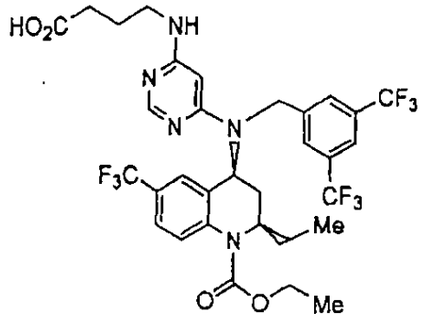


Tabla 24

Ejemplo	R^{11}	Propiedades físicas, etc.
162		MS (m/z): 694 $[M+H]^+$
163		MS (m/z): 708 $[M+H]^+$

Ejemplo 164



Los compuestos de comienzo correspondientes fueron tratados de manera similar a la del Ejemplo 124 para dar el compuesto del Ejemplo 164. MS (m/z): 722 $[M+H]^+$

Ejemplo 165

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,5 g) y 3-bromobencildeido (974 mg) fueron disueltos en 1,2-

dicloroetano (15 ml), y a los mismos fueron agregados triacetoxi borohidruro de sodio (2,14 g) a temperatura ambiente. La mezcla fue agitada durante 3 horas, y fueron agregados a los mismos una solución acuosa de carbonato de hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 19:1→7:3) para dar etil éster de ácido (2R,4S)-4-(3-bromobencil)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,45 g). MS (m/z): 485/487 $[M+H]^+$

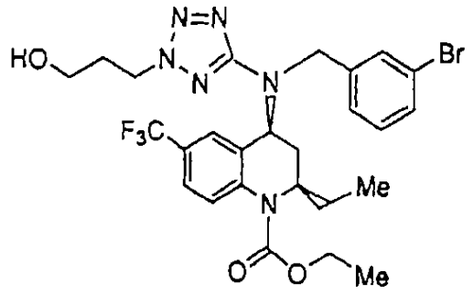
(2) Etil éster de ácido (2R,4S)-4-(3-Bromobencil)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,32 g), bromociano (609 mg), y carbonato hidrógeno de sodio (1,22 g) fueron suspendidos en etanol (30 ml), y la mezcla fue agitada toda la noche a temperatura ambiente. A la solución de reacción fue agregada una solución acuosa de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida para dar etil éster de ácido (2R,4S)-4-[ciano-(3-bromobencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,43 g). MS (m/z): 527/529 $[M+H_2O]^+$

(3) Etil éster de ácido (2R,4S)-4-[Ciano-(3-bromobencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,43 g), azida sódica (3,12 g), y cloruro de amonio (2,56 g) fue disuelto en N,N-dimetilformamida (20 ml), y la mezcla fue agitada toda la noche a 95°C. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida para dar etil éster de ácido (2R,4S)-4-[(3-bromobencil)-(tetrazol-5-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,58 g). MS (m/z): 553/555 $[M+H]^+$

(4) Etil éster de ácido (2R,4S)-4-[(3-Bromobencil)-(tetrazol-5-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg), 2-bromoetanol (271 mg), y carbonato de potasio (375 mg) fueron disueltos en N,N-dimetilformamida (3 ml), y la mezcla fue agitada toda la noche a 50°C. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→2:3) para dar etil

éster de ácido (2R,4S)-4-{(3-bromobencil)-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (394 mg). MS (m/z): 597/599 $[M+H]^+$

Ejemplo 166



Los compuestos de comienzo correspondientes fueron tratados de manera similar a la del Ejemplo 165-(4) para dar el compuesto del Ejemplo 166, MS (m/z): 611/613 $[M+H]^+$

Ejemplo 167

(1) Etil éster de ácido (2R,4S)-4-[(3-Bromobencil)-(tetrazol-5-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg), glicidol (89 µl), y trifenilfosfina (711 mg) fueron disueltos en tetrahidrofurano (3 ml), y a los mismos fueron agregados 40% dietil éster de ácido azodicarboxílico en tolueno (1180 mg) a temperatura ambiente, y la mezcla fue agitada durante 15 minutos. A la solución de reacción fueron agregados agua y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue

purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 19:1→3:2) para dar etil éster de ácido (2R,4S)-4-[(3-bromobencil)-(2-oxiranilmetil-2H-tetrazol-5-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (347 mg). MS (m/z): 609/611 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[(3-Bromobencil)-(2-oxiranilmetil-2H-tetrazol-5-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (330 mg) y tetrahidroxazina (1 ml) fueron disueltos en etanol (3 ml), y la mezcla fue agitada toda la noche a temperatura ambiente. A la solución de reacción fueron agregados agua y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 2:3→0:1) para dar etil éster de ácido (2R,4S)-4-{(3-bromobencil)-[2-(2-hidroxi-3-morfolin-4-ilpropil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (315 mg). MS (m/z): 696/698 $[M+H]^+$

Ejemplo 168

(1) Etil éster de ácido (2R,4S)-4[(3-Bromobencil)-(tetrazol-5-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg) fue tratado de una manera similar a la

del Ejemplo 167-(1) para dar etil éster de ácido (2R,4S)-4-{(3-bromobencil)-[2-(2-metilsulfaniletil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (524 mg). MS (m/z): 627/629 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{(3-Bromobencil)-[2-(2-metilsulfaniletil)-2H-tetrazol-5-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (520 mg) fue tratado de una manera similar a la del Ejemplo 50 para dar etil éster de ácido (2R,4S)-4-{(3-bromobencil)-[2-(2-metilsulfoniletil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (474 mg). MS (m/z): 659/661 $[M+H]^+$

Ejemplos 169-172

Los compuestos de comienzo correspondientes fueron tratados en una manera similar a la del Ejemplo 10 para dar los compuestos enumerados en la Tabla 25.

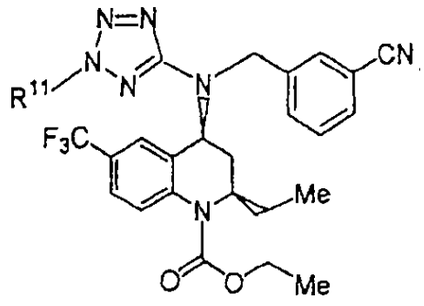
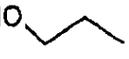
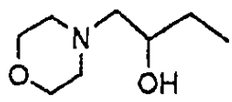
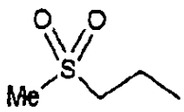


Tabla 25

Ejemplo	R^{11}	Propiedades físicas, etc.
169		MS (m/z): 544 $[M+H]^+$

170		MS (m/z): 558 $[M+H]^+$
171		MS (m/z): 643 $[M+H]^+$
172		MS (m/z): 606 $[M+H]^+$

Ejemplo 173

(1) (2R*,4S*)-(4-benciloxicarbonilamino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (112,8 g) fue disuelta en etanol (1000 ml), y a los mismos fue agregado 10% paladio-carbono (5,64 g), y la mezcla fue agitada toda la noche a temperatura ambiente dentro de una atmósfera de hidrógeno. El catalizador (10% paladio-carbono) fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. Al residuo fue agregado hexano, y los precipitados en forma de cristales fueron reunido por filtración para dar (2R*,4S*)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (70,3 g). MS (m/z): 245 $[M+H]^+$

(2) (2R*,4S*)-4-amino-2-etil-6-trifluorometil-3,4-dihicro-2H-quinolina (70,0 g) fue disuelto en tetrahidrofurano (500 ml), y a los mismos fueron agregados dicarbonato de di-terc-butilo (68,2 g). La mezcla fue agitada a temperatura ambiente toda una noche, y fue concentrada bajo presión reducida. Al residuo fue agregado hexano, y los precipitados en forma de

cristal fueron recolectados por filtración para dar (2R*,4S*)-4-terc-butoxicarbonilamino-(2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (90,7 g). MS (m/z): 345 $[M+H]^+$

(3) (2R*,4S*)-4-Terc-butoxicarbonilamino(2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (90,58 g) y trietilamina (44 ml) fueron disueltos en cloruro de metileno (900 ml), y a los mismos fueron agregados trifosgeno (31,2 g) bajo enfriamiento con hielo. La solución de reacción fue agitada a temperatura ambiente durante una hora, y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (900 ml), y fueron agregados a los mismos alcohol bencílico (54,4 ml), y hidruro de sodio (60%; 20,2 g) bajo enfriamiento con hielo. La mezcla fue agitada a la misma temperatura durante 3 horas. A la mezcla de reacción fueron agregados agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo fue cristalizado del diisopropil éter para dar bencil éster de ácido (2R*,4S*)-4-terc-butoxicarbonilamino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (104,7 g). MS (m/z): 496 $[M+H_2O]^+$

(4) Bencil éster de ácido (2R*,4S*)-4-terc-butoxicarbonilamino-2-etil-6-trifluorometil-3,4-dihidro-2H-

quinolin-1-carboxílico (104,5 g) fue disuelto en cloroformo (500 ml), y fueron agregados a los mismos una solución 4N de ácido clorhídrico en acetato de etilo (500 ml) a temperatura ambiente. La mezcla fue agitada durante 30 minutos, y fue concentrada bajo presión reducida. Al residuo fue agregado diisopropil éter, y los precipitados en forma de cristal fueron recolectados por filtración para dar hidrocloruro de benciléster de ácido (2R*,4S*)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (88,0 g). MS (m/z): 379 $[M+H]^+$

(5) Hidrocloruro de bencil éster de ácido (2R*,4S*)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (25,0 g) fue disuelto en una mezcla de acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante (23 g) y 5-bromo-2-cloropirimidina (29,3 g) fueron disueltos en 1,4-dioxano (100 ml), y a los mismos fueron agregados N,N-diisopropiletilamina (32 ml), y la mezcla fue agitada toda la noche. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue

purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 6:1→2:1) para dar bencil éster de ácido (2R*,4S*)-4-(5-bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (24,0 g). MS (m/z): 535/537 $[M+H]^+$

(6) Bencil éster de ácido (2R*,4S*)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (13 g) fue tratado de una manera similar a la del Ejemplo 1-(2) para dar bencil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (20,6 g). MS (m/z): 761/763 $[M+H]^+$

(7) Bencil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (18,3 g) fue tratado de una manera similar a la del Ejemplo 1-(3) para dar bencil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-3,4-dihidro-6-trifluorometil-2H-quinolin-1-carboxílico (11,2 g). MS (m/z): 768 $[M+H]^+$

(8) Bencil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (11,2 g) fue tratado de una manera similar a la del Ejemplo 150 para dar (2R*,4S*)-4-

{[3,5bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (8,9 g). MS (m/z): 634 $[M+H]^+$

Ejemplo 174

(2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (500 mg) y trietilamina (132 µl) fueron disueltos en cloruro de metileno (5 ml), y a los mismos fueron agregados trifosgeno (94 mg) a temperatura ambiente, y la mezcla fue agitada durante una hora. La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue separado dentro de acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (5 ml), y glicol etilénico (0,5 ml), fueron agregados a los mismos trietilamina (295 ml) y 4-dimetilaminopiridina (26 mg). La mezcla fue agitada toda la noche a temperatura ambiente. La solución de reacción fue separada dentro de acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel

de sílice (hexano:acetato de etilo = 3:1→2:3) para dar 2-hidroxietil éster de ácido (2R*,4S*)4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (430 mg). MS (m/z): 722 $[M+H]^+$

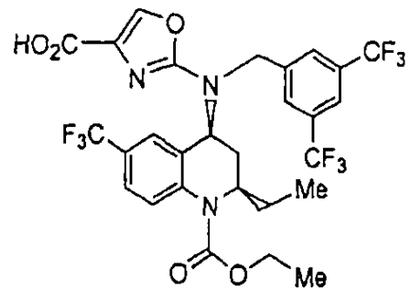
Ejemplo 175

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,28 g), etil éster de ácido 2-cloroxazol-4-carboxílico (1,44 g) y diisopropiletilamina (1,42 ml) fueron disueltos en 1,4-dioxano (10 ml), y la mezcla fue agitada toda la noche a 130°C. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-(4-etoxicarboniloxazol-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,13 g). MS (m/z): 456 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-(4-Etoxicarboniloxazol-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,12 g) fue tratado de una manera similar a la

del Ejemplo 1-(2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis-(trifluorometil)bencil]-(4-etoxicarboniloxazol-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (928 mg). MS (m/z): 682 $[M+H]^+$

Ejemplo 176



Los compuestos de comienzo correspondientes fueron tratados de manera similar a los del Ejemplo 124 para dar el compuesto del Ejemplo 176. MS (m/z): 654 $[M+H]^+$

Ejemplo 177

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (32,25 g), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio (1,012 g), acetado de potasio (13,6 g), y bis(pinacolato)diborono (17,56 g) fue disuelto en dimetilsulfóxido (200 ml), y la mezcla fue agitada a 80°C dentro de una atmósfera de nitrógeno durante una hora. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo

presión reducida. El residuo resultante fue disuelto en el tetrahidrofurano (100 ml), y a los mismos fueron agregados de manera lenta una solución acuosa al 30% de agua oxigenada (70 ml) bajo enfriamiento con hielo. Después de pasada una hora, una solución acuosa saturada de tiosulfato de sodio fue agregada a la mezcla, y el exceso de agua oxigenada fue evaporado. La mezcla fue separada en agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 5:1→3:1) para dar etil éster de ácido (2R,4S)-4-{{3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (19,22 g). MS (m/z): 637 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (6,5 g) y etil éster de ácido 4-bromobutílico (2,19 g) fue disuelto en N,N-dimetilformamida (50 ml), y a los mismos fueron agregados carbonato de potasio (1,69 g), y la mezcla fue agitada toda la noche a 45°C. Fueron agregados acetato de etilo y agua a la mezcla, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo

resultante fue purificado por cromatografía en columna ce gel de sílice (hexano:acetato de etilo = 95:5→3:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)benci]}-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (6,52 g). MS (m/z): 751 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (6,5 g) fue disuelto en etanol (65 ml), y a los mismos fue agregada una solución 2N acuosa de hidróxido de sodio (13 ml). La mezcla fue agitada toda la noche a temperatura ambiente. La solución de reacción fue concentrada bajo presión reducida, y al residuo fueron agregados acetato de etilo y una solución acuosa 1N de ácido clorhídrico, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol 1:0→95:5) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (6,16 g). MS (m/z): 723 $[M+H]^+$

Ejemplo 178

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) fue disuelto en etanol (3 ml), y fue agregada a los mismos una solución acuosa 2N de hidróxido de sodio (207 µl). La solución de reacción fue concentrada a sequedad bajo presión reducida para dar sal de sodio de etil éster de ácido (2R,4S)-4{[3,5-bis(trifluorometil)benci]]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (308 mg). MS (m/z): 721 $[M-Na]^-$

Ejemplo 179

Sal de sodio de etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (258 mg) fue suspendida en agua (10 ml), y a los mismos fue agregada una solución de cloruro de calcio (154 mg) en agua (0,6 ml), y la mezcla fue agitada toda la noche a temperatura ambiente. Fueron agregados cloroformo y agua a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue disuelto en acetato de etilo, y a los mismos fueron agregados n-hexano. Los cristales precipitados fueron

recolectados por filtración para dar sal hemicalcio de etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (169 mg). MS (m/z): 721 $[M-1/2Ca]^-$

Ejemplo 180

Etil éster de ácido (2R,4S)-4-{[3,5-Bis-(trifluorometil)bencil]-[5-(3-carboxipropoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (250 mg) fue disuelto en etanol (2 ml), y a los mismos fue agregada una solución 2N acuosa de hidróxido de potasio (173 µl). La solución de reacción fue concentrada a sequedad bajo presión reducida para dar sal de potasio de etil éster ácido (2R,4S)4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (256 mg). MS (m/z): 721 $[M-K]^-$

Ejemplos 181-186

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 177 (2) para dar los compuestos enumerados en la Tabla 26.

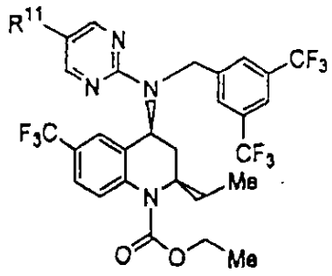
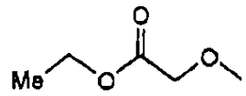
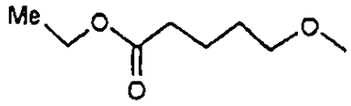
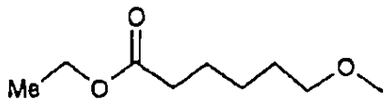
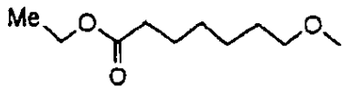
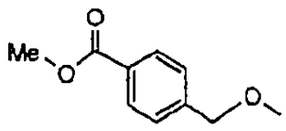
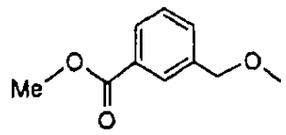


Tabla 26

Ej. No.	R^{11}	Propiedades físicas, etc.
181		MS (m/z): 723 $[M+H]^+$
182		MS (m/z): 765 $[M+H]^+$
183		MS (m/z): 779 $[M+H]^+$
184		MS (m/z): 793 $[M+H]^+$
185		MS (m/z): 785 $[M+H]^+$
186		MS (m/z): 785 $[M+H]^+$

Ejemplo 187

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,0 g) fue disuelto en N,N-dimetilformamida (30 ml), y fueron agregados a los mismos bromoacetato de etilo (520 µl), carbonato de potasio (650 mg). La mezcla fue agitada a temperatura ambiente durante 3,5 horas. Fueron agregados agua y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada,

fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 19:1→41:9) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-etoxicarbonil-metoxipirmidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,07 g). MS (m/z): 723 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-etoxicarbonilmetoxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,07 g) fue disuelto en etanol (30 ml), y a los mismos fue agregada de forma lenta una solución acuosa 1N de hidróxido de sodio. La mezcla fue agitada durante 2,5 horas, y fueron agregados a los mismos una solución 6N de ácido clorhidrico y acetato de etilo. La mezcla fue separada, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-carboximetoxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,83 g). MS (m/z): 695 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-carboximetoxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxilico (200 mg) fue disuelto en tetrahidrofurano (4 ml); y fueron agregados a los mismos hidrocloruro de aminoacetato de etilo (48 mg), dihidrato de 1-hidroxibenzotriazol (47 mg), hidrocloruro de 1-etil-3-(3-dimetilamino-propil)carbodiimida (66 mg), y trietilamina (49 µl), y la mezcla fue agitada a temperatura ambiente durante una hora. Fueron agregados agua y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-{5-[(etoxicarbonilmetilcarbamoil)metoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (165 mg). MS (m/z): 780 $[M+H]^+$

Ejemplos 188-190

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 187 (3) para dar los compuestos enumerados en la Tabla 27.

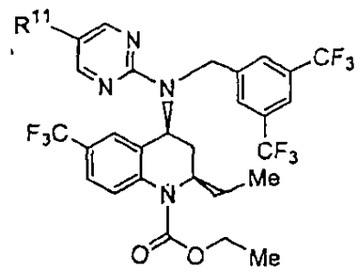
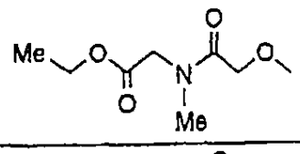
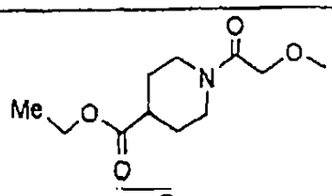
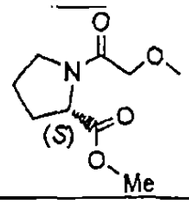


Tabla 27

Ej. No.	R^{11}	Propiedades físicas, etc.
188		MS (m/z): 794 $[M+H]^+$
189		MS (m/z): 834 $[M+H]^+$
190		MS (m/z): 806 $[M+H]^+$

Ejemplo 191

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) fue disuelto en tetrahidrofurano (4 ml), y fueron agregados a los mismos (2S,4R)-1-benciloxicarbonil-2-metoxicarbonil-4-hidroxipirolidina (395 mg) y trifenilfosfina (740 mg). A la mezcla fue agregada de forma lenta una solución de azodicarboxilato de dietilo en tolueno al 40% (1,23 ml) bajo enfriamiento con hielo, y la mezcla fue

agitada toda la noche a temperatura ambiente. Fueron agregados agua y acetato de etilo a la mezcla, y ésta fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-{5-[(S)-2-((S)-metoxicarbonil)-1-benciloxicarbonilpirolidin-4-iloxi]pirimidin-2-il}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (543 mg) producto en bruto. MS (m/z): 898 $[M+H]^+$

(2) El etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-[(S)-2((S)metoxicarbonil)-1-benciloxicarbonilpirolidin-4-iloxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,39 g) en bruto fue disuelto en metanol (15 ml), y a éstos fue agregado 10% paladio-carbono (300 mg). La mezcla fue agitada en atmósfera de hidrógeno durante 3 horas, fue filtrada, y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 3:2→2:3→0:1) para dar etil éster de ácido (2R,4S)-4{[3,5-bis(trifluorometil)bencil]-{5-[(S)-2-((S)-metoxi-

carbonil)pirolidin-4-iloxi]pirimidin-2-il})amino-2-etil-5-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (667 mg). MS (m/z): 764 $[M+H]^+$

Ejemplo 192

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-[(S)-2-((S)-metoxicarbonil)pirolidin-4-iloxi)pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en tetrahidrofurano (5 ml), y fueron agregados a los mismos cloruro de acetileno (44 µl) y trietilamina (88 µl) bajo enfriamiento con hielo. La mezcla fue agitada a temperatura ambiente durante 4 horas, y fue separada en una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 3:2→2:3) para dar etil éster de ácido (2R,4S)-4([3,5-bis(trifluorometil)bencil]-{5-[(S)-2-((S)-metoxicarbonil)-1-acetilpirolidin-4-iloxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (212 mg). MS (m/z): 806 $[M+H]^+$

Ejemplo 193

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,5 g) fue disuelto en N,N-dimetilformamida (20 ml), y fueron agregados a los mismos 2-bromoetanol (1,25 ml) y carbonato de potasio (490 mg), y la mezcla fue agitada toda la noche a 60°C. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (493 mg). MS (m/z): 681 $[M+H]^+$

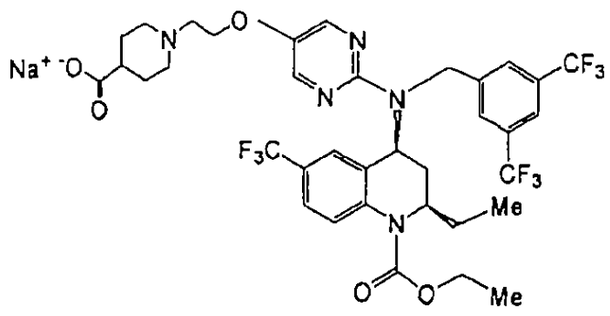
(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (493 mg) fue disuelto en cloruro de metileno (10 ml), y fueron agregados a los mismos trifenilfosfina (380 mg) y tetrabromuro de carbono (480 mg). La mezcla fue agitada a temperatura ambiente durante 30 minutos, y fueron agregados a los mismos una solución acuosa saturada de carbonato

hidrógeno de sodio y cloroformo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-bromoetoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (298 mg). MS (m/z): 743/745 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-bromoetoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (298 mg) fue disuelto en N,N-dimetilformamida (5 ml), y fueron agregados a los mismos etil éster de ácido piperidin-4-carboxílico (185 µl) y carbonato de potasio (166 mg), y la mezcla fue agitada a temperatura ambiente durante 1,5 hora. La mezcla fue agitada a 60°C durante 2,5 horas. Fueron agregados una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 1:1→1:4) para dar etil

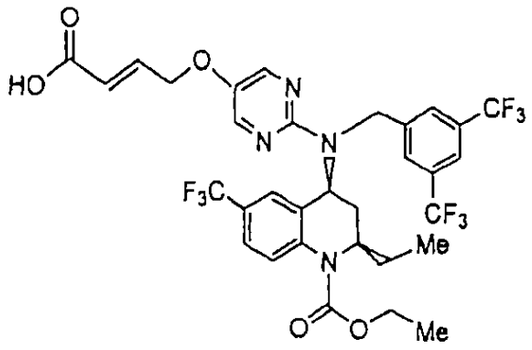
éster de ácido (2R,4S)-4-([3,5bis(trifluorometil)bencil)-{5-[2-(4-etoxicarbonilpiperidin-1-il)etoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (245 mg). MS (m/z): 820 $[M+H]^+$

Ejemplo 194



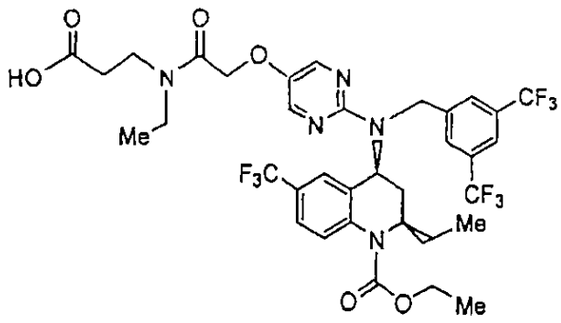
Los compuestos de comienzo correspondientes fueron tratados en una manera similar al Ejemplo 177 (3) y Ejemplo 178 para dar el compuesto del Ejemplo 194. MS (m/z): 790 $[M-Na]^-$

Ejemplo 195



Los compuestos de comienzo correspondientes fueron tratados en una manera similar al Ejemplo 177 (2)-(3) para dar el compuesto de Ejemplo 195. MS (m/z): 721 $[M+H]^+$

Ejemplo 196



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 187 (3) y Ejemplo 177 (3) para dar el compuesto de Ejemplo 196. MS (m/z): 794 $[M+H]^+$

Ejemplos 197-208

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 177 (3) para dar los compuestos como los enumerados en la Tabla 28.

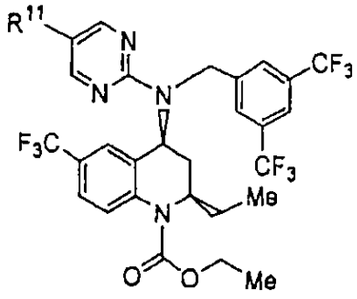
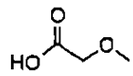
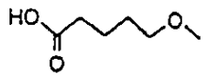
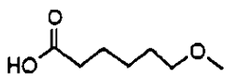
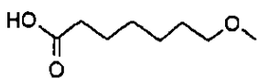
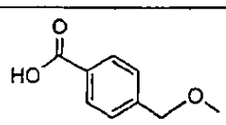
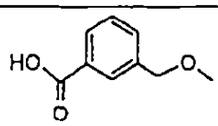
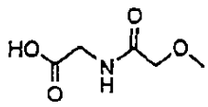
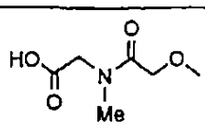
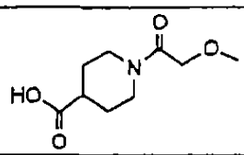
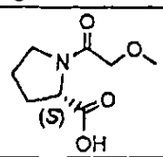
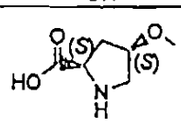
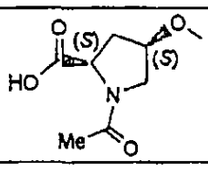


Tabla 28

Ej. No.	R^{11}	Propiedades físicas, etc.
197		MS (m/z): 695 $[M+H]^+$
198		MS (m/z): 737 $[M+H]^+$
199		MS (m/z): 751 $[M+H]^+$
200		MS (m/z): 765 $[M+H]^+$
201		MS (m/z): 771 $[M+H]^+$
202		MS (m/z): 771 $[M+H]^+$
203		MS (m/z): 752 $[M+H]^+$
204		MS (m/z): 766 $[M+H]^+$
205		MS (m/z): 806 $[M+H]^+$
206		MS (m/z): 792 $[M+H]^+$
207		MS (m/z): 750 $[M+H]^+$
208		MS (m/z): 792 $[M+H]^+$

Ejemplo 209

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) fue disuelto en tetrahidrofurano (3 ml), y fueron agregados a los mismos terc-butóxido de potasio (53 mg) y β-propiolactona (30 µl) a la temperatura ambiente. La solución de reacción fue agitada a la temperatura ambiente de noche, y fueron agregados a los mismos acetato de etilo y 1N ácido clorhídrico, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, y fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en una mezcla de tetrahidrofurano y metanol (5:1, 2 ml), y fueron agregados a los mismos una solución 2M de trimetilsilildiazometano en el hexano (353 µl). Treinta minutos después de esto, la solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue purificado por la cromatografía en columna de gel NH-sílice (hexano:acetato de etilo = 95:5→>3:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-metoxicarboniletoxi)pirimidin-2-il]}-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (27 mg). MS (m/z): 723 $[M+H]^+$

Ejemplo 210

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (900 mg) fue disuelto en tetrahidrofurano (9 ml), y fueron agregados a los mismos terc-butóxido de potasio (158 mg) y β-propiolactona (89 µl) a la temperatura ambiente. La solución de reacción fue agitada a la temperatura ambiente de noche, y fueron agregados a los mismos acetato de etilo y 1N ácido clorhídrico, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-carboxietoxi)pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (178 mg). MS (m/z): 709 $[M+H]^+$

Ejemplo 211

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifiuorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg) fue disuelto en N,N-dimetilformamida (5 ml), y fueron agregados a los mismos 2-(2-cloroetoxi)ethanol (830

µl), y carbonato de potasio (1,09 g), y la mezcla fue agitada a la temperatura ambiente durante 3 horas. La mezcla de reacción fue agitada toda la noche a 60°C. La solución de reacción fue enfriada a la temperatura ambiente, y la mezcla fue separada en agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificada por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar éster de etilo de ácido (2R,4S)-4-({[3,5-bis(trifluorometil)bencil]-{5-[2-(2-hidroxietoxi)etoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (710 mg) como un producto en bruto. MS (m/z): 725 $[M+H]^+$

(2) El etil éster de ácido (2R,4S)-4-({[3,5-bis(trifluorometil)bencil]-{5-[2-(2-hidroxietoxi)etoxi)pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (706 mg) en bruto fue disuelto en cloruro de metileno (10 ml), y fueron agregados a los mismos 1,1,1-tris(acetoxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona (826 mg), y la mezcla fue agitada toda la noche a temperatura ambiente. Se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica

fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión recucida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-formilmetoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (190 mg). MS (m/z): 723 $[M+H]^+$

Ejemplo 212

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil)-{5-[2-(2-oxoetoxi)etoxi)pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (160 mg) fue disuelto en una mezcla de terc-butanol (3 ml) y agua (0,8 ml), y fueron agregados a los mismos dihidrato dihidrógeno de fosfato de potasio (41,4 mg), la clorita de sodio (85 mg), y 2-metil-2-buteno (103 µl), y la mezcla fue agitada a la temperatura ambiente, durante 2 horas. A la solución de reacción se agregan 1N ácido clorhídrico y acetato de etilo bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por la cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar etil

éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil][5-(2-carboximetoxietoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (132 mg).
MS (m/z): 739 $[M+H]^+$

Ejemplo 213

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg) fue disuelto en N,N-dimetilformamida (5 ml), y fueron agregados a los mismos bencil éster de ácido 2-cloroetilcarbámico (402 mg) y carbonato de potasio (260 mg), y la mezcla fue agitada toda la noche a 80°C. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[5-(2-benciloxicarbonilaminoetoxi)pirimidin-2-il]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (249 mg).
MS (m/z): 814 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[5-(2-benciloxicarbonilaminoetoxi)pirimidin-2-il]-[3,5-

bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (240 mg) fue disuelto en metanol (5 ml), y fueron agregados a los mismos 10% paladio-carbono (100 mg), y la mezcla fue agitada bajo atmósfera de hidrógeno durante 2 horas. La solución de reacción fue filtrada y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 7:3→2:3) para dar etil éster de ácido (2R,4S)-4-{[5-(2-aminoetoxi)pirimidin-2-il]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (167 mg). MS (m/z): 680 $[M+H]^+$

Ejemplo 214

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (975 mg) fue disuelto en N,N-dimetilformamida (4,5 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 70 mg) bajo enfriamiento con hielo, y la mezcla fue agitada durante 10 minutos. Fue agregado a la solución de reacción4-bromobutironitrilo (0,2 ml), y la mezcla fue agitada a la temperatura ambiente durante una hora. A la solución de reacción se agregan agua y acetato de etilo bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre

sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,1 g). MS (m/z): 704 $[M+H]^+$

Ejemplo 215

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg), azida de sodio (462 mg), y cloruro de amonio (380 mg) fue disuelto en N,N-dimetilformamida (1 ml), y la mezcla fue agitada a 120°C durante 27 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos 1N ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar etil éster de ácido (2R,4S)-4{[3,5-bis(trifluorometil)benzyi]-{5-[3-(tetrazol-5-il)propoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (169 mg).

MS (m/z): 747 $[M+H]^+$

Ejemplo 216

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (700 mg), hidrocloruro de hidroxilamina (140 mg) y carbonato de sodio (212 mg) fueron disueltos en etanol (3 ml), y la mezcla permaneció a reflujo durante 41 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 7:3→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-[3-(N-hidroxicarbamimidoil)propoxi)pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (502 mg). MS (m/z): 737 $[M+H]^+$

Ejemplo 217

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-{5-[3-(N-hidroxicarbamimidoil)propoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg), y 1,1'-carbonildiimidazol (66 mg) fueron disueltos en

acetonitrilo (1,5 ml), y la mezcla fue agitada a 60°C durante 16,5 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 7:3→1:1) para dar etil éster de ácido (2R,4S)-4-([3,5bis(trifluorometil)bencil]-{5-[3-(5-oxo-4,5-dihidro[1,2,4]oxadiazol-3-il)propoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (115 mg). MS (m/z): 763 $[M+H]^+$

Ejemplo 218

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-{5-[3-(N-hidroxicarbamimidoil)propoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (240 mg) y piridina (106 µl), fue disuelto en tetrahidrofurano (7,5 ml), y fueron agregados a los mismos por gotas una solución de cloruro de tionilo (48 µl), en cloruro de metileno (3 ml), y la mezcla fue agitada durante 2 horas y 40 minutos. La solución de reacción fue concentrada bajo presión reducida, y fueron agregados a los mismos agua y acetato de etilo, y la

mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-({[3,5-bis(trifluorometil)bencil]-{5-[3-(2-oxo-3H-[1,2,3,5]-oxotiazol-4-il)propoxi]pirimidin-2-il}}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (181 mg). MS (m/z): 783 $[M+H]^+$

Ejemplo 219

Cloruro de 3-cloropropan-1-sulfonilo (0,38 ml) fue disuelto en cloruro de metileno (15 ml), y el gas de amoníaco fue soplado en la mezcla durante 15 minutos. La solución de reacción fue agitada toda la noche, y el cloruro de amonio resultante fue eliminado por filtración. El filtrado fue concentrado, y el 3-cloropropan-1-sulfonamida resultante y etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg), yoduro de potasio (1,3 g), e hidróxido de potasio (352 mg) fueron disueltos en dimetilsulfóxido (4 ml), y la mezcla fue agitada a 60°C durante 24 horas. La mezcla fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada,

fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→1:1) para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil)-[5-(3-sulfamoilpropoxi)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (22 mg). MS (m/z): 758 $[M+H]^+$

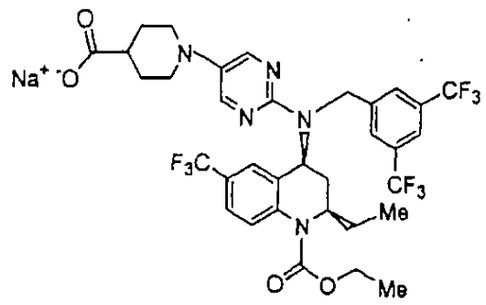
Ejemplo 220

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifiuorometil-3,4-dihidro-2-H-quinolin-1-carboxílico (300 mg) fue disuelto en tetrahidrofurano (5 ml), y fueron agregados a los mismos etil 4-(hidroximetil)ciclohexilacetato (141 mg) y trifenilfosfina (370 mg). A la mezcla fue agregada por gotas una solución 40% de azodicarboxilato de dietilo en tolueno (600 µl) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 2,5 horas. Se agregan agua y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 19:1→44:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-

etoxicarbonilmetilciclohexilmetoxi)pirimidin-2-il]}aminc-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (275 mg). MS (m/z): 819 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-etoxicarbonilmetilciclohexilmetoxi)pirimidin-2-il]}aminc-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (220 mg) fue disuelto en etanol (5 ml), y fueron agregados a los mismos por gotas una solución acuosa 1N de hidróxido de sodio (1 ml), y la mezcla fue agitada toda la noche a temperatura ambiente. A la mezcla se agregan 1N ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo: metanol = 1:0→9:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-carboximetilciclohexil-metoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (181 mg). MS (m/z): 791 $[M+H]^-$

Ejemplo 221



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 178 para dar el compuesto de Ejemplo 221. MS (m/z): 746 [M-Na]$^-$

Ejemplos 222-224

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 1(3) para dar los compuestos como los enumerados en la Tabla 29.

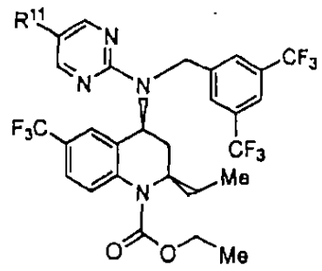
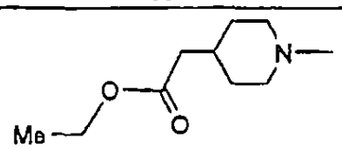
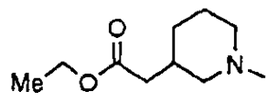
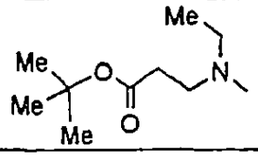


Tabla 29

Ej. No.	R^{11}	Propiedades físicas, etc.
222		MS (m/z): 790 $[M+H]^+$
223		MS (m/z): 790 $[M+H]^+$
224		MS (m/z): 792 $[M+H]^+$

Ejemplos 225-226

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 177 (3) para dar los compuestos como los enumerados en la Tabla 30.

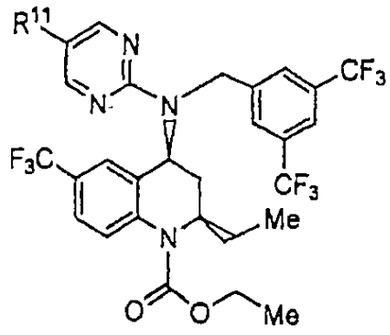
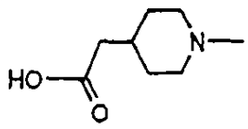
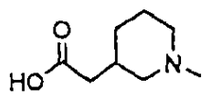


Tabla 30

Ej. No.	R^{11}	Propiedades físicas, etc.
225		MS (m/z): 762[M+H]$^+$
226		MS (m/z): 762[M+H]$^+$

Ejemplo 227

Etil éster de ácido (2R,4S)-4-[[3,5-Bis(trifluorometil)bencil]-(5-[etil-(2-terc-butoxi-carboniletil)]aminopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (70 mg) fue disuelto en 4N cloruro de hidrógeno en acetato de etilo (0,5 ml), y la mezcla fue agitada a la temperatura ambiente durante 3 horas. Fue agregado a la solución de reacción una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica

fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida para dar etil éster de ácido (2R,4S)-4-[[3,5-bis(trifluorometil)bencil]-(5-{[etil-(2-carboxietil)-amino}pirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (65 mg). MS (m/z): 736 $[M+H]^-$

Ejemplo 228

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-iodopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,0 g), yoduro de cobre (13 mg), carbonato de potasio (370 mg), etilén glicol (0,15 ml), y 4-mercaptobutanol (0,14 ml) fue disuelto en alcohol isopropílico (1,5 ml), y la mezcla fue agitada a 80°C bajo atmósfera de nitrógeno durante 15 horas. La mezcla fue enfriada a la temperatura ambiente, y fueron agregados a los mismos acetato de etilo. Los materiales insolubles fueron eliminados por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-hidroxibutilsulfanil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (705 mg). MS (m/z): 725 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-hidroxibutilsulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg) fue disuelto en cloroformo (2 ml), y fueron agregados a los mismos el ácido m-cloroperbenzoico (75%, 636 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante una hora, y fueron agregados a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 7:3→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-hidroxibutilsulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin1-carboxílico (309 mg). MS (m/z): 757 $[M+H]^+$

(3) etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-hidroxibutilsulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) y 1,1,1-tris(acetoxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona (269 mg) fue disuelto en cloruro de metileno (2 ml), y la

mezcla fue agitada durante 2,5 horas. Se agregan agua y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropilsulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (103 mg).
MS (m/z): 771 $[M+H]^+$

Ejemplo 229

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3 g), etil éster de ácido 2-cloro-4-metiltiazol-5-carboxílico (5,85 g) y diisopropiletilamina (3,3 ml) fueron disueltos en 1,4-dioxano (25 ml), y la mezcla fue agitada a 130°C durante una semana. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados agua y acetato de etilo a los mismos, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 6:1→4:1) para dar etil

éster de ácido (2R,4S)-4-(5-etoxicarbonil-4-metiltiazol-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,93 g). MS (m/z): 486 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-(5-Etoxicarbonil-4-metiltiazol-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,9 g) fue disuelto en N,N-dimetilformamida (20 ml), y fueron agregados a los mismos hidruro de sodio (62,7%, 282 mg) bajo enfriamiento con hielo. La mezcla de reacción fue agitada a la temperatura ambiente durante 30 minutos, y fueron agregados a los mismos bromuro de 3,5-bis(trifluorometil)bencilo (1,56 ml) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 3 horas, y fueron agregados una solución de ácido cítrico acuosa saturada y acetato de etilo a los mismos, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-etoxicarbonil-4-metiltiazol-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,62 g). MS (m/z): 712 $[M+H]^+$

Ejemplo 230

Etil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-(5-etoxicarbonil-4-metiltiazol-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (250 mg) y monohidrato de hidróxido de litio (147 mg) fue disuelto en una mezcla de etanol (5 ml) y una solución 2N de hidróxido de sodio acuosa (703 µl), y la mezcla fue agitada a 70°C durante 2 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fue acidificada con solución 2N ácido clorhídrico acuoso. Subsiguientemente, a la mezcla se agrega el acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida, El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→19:1) para dar éster de etilo de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-carboxi-4-metiltiazol2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (189 mg). MS (m/z): 684 $[M+H]^+$

Ejemplo 231

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (10,0 g), 2,5-dibromopiridin (15 g), tris(dibencilidenacetona)dipaladio (2,9 g), 2-diciclohexilfosfino-2'-(N,N-dimetilamino)bifenilo (2,5 g) y terc-butóxido de sodio (6,1 g) fue disuelto en

tolueno (100 ml), y la mezcla fue agitada a 80°C durante 15 horas bajo atmósfera de nitrógeno. La mezcla fue enfriada a temperatura ambiente, y fueron agregados agua y acetato de etilo a los mismos, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, y fueron agregados a los mismos gel de NH-sílice, y la mezcla fue filtrada. El filtrado fue concentrado bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-(5-bromopiridin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,56 g). MS (m/z): 472/474 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-(5-Bromopiridin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxilico (2,4 g) fue disuelto en N,N-dimetilformamida (15 ml), y fueron agregados a los mismos hidruro de sodio (40%, 335 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 30 minutos, y fueron agregados a los mismos bromuro de 3,5-bis(trifluorometilbencilo (1,1 ml). La mezcla fue agitada a la temperatura ambiente durante 5 horas. A la mezcla fueron agregados agua y dietil éter bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con 1N ácido clorhídrico, agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo

resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,72 g). MS (m/z): 698/700 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopiridin-2-il)}-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,72 g), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (54 mg), acetato de potasio (725 mg) y bis(pinacolato)diboro (938 mg) fueron disueltos en dimetilsulfóxido desaereado (7 ml), y la mezcla fue agitada a 80°C durante una hora. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados agua y acetato de etilo a los mismos, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (7,5 ml), y fueron agregados a los mismos una solución 30% de agua oxigenada acuosa (2,8 ml) bajo enfriamiento con hielo, y la mezcla fue agitada durante 3 horas. Se agregan una solución de tiosulfato de sodio acuosa saturada y acetato de etilo a la mezcla bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue

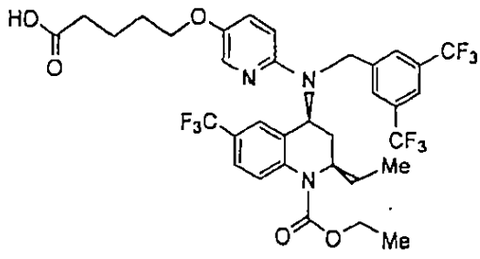
concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (851 mg). MS (m/z): 636 $[M+H]^+$

(4) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil](5-hidroxipiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en N,N-dimetilformamida (1,5 ml), y fueron agregados a los mismos hidruro de sodio (15 mg) bajo enfriamiento con hielo. La mezcla fue agitada durante 15 minutos, y fueron agregados a los mismos etil éster de ácido 4-bromobutírico (69 µl), y la mezcla fue agitada a la temperatura ambiente durante 1,5 hora. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)piridin-2-il]}amino-2-etil-6-

trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (132 mg). MS (m/z): 750 $[M+H]^+$

(5) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (120 mg) fue disuelto en etanol (0,8 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (0,24 ml), y la mezcla fue agitada durante 3 horas. Fue agregado a la solución de reacción una solución 2N de ácido clorhídrico (0,24 ml) y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 7:3→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (105 mg). MS (m/z): 722 $[M+H]^+$

Ejemplo 232



Los compuestos de comienzo correspondientes fueron

tratados de manera similar al Ejemplo 231 (4)-(5) para dar el compuesto de Ejemplo 232. MS (m/z): 736 $[M+H]^+$

Ejemplo 233

(1) Etil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (18 g) fue disuelto en tetrahidrofurano (180 ml), y fueron agregados a los mismos dicarbonato de di-terc-butilo (24,8 g) y una cantidad catalítica de dimetilaminopiridina, y la mezcla fue agitada toda la noche a la temperatura ambiente. A la mezcla se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 8:1) para dar etil éster de ácido (2R,4S)-4-[(5-bromopirimidin-2-il)-terc-butoxicarbonil]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (22,5 g). MS (m/z): 573/575 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[(5-Bromopirimidin-2-il)-terc-butoxicarbonil]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (22,5 g) fue disuelto en 1,4-dioxano (110 ml), y fueron agregados a los mismos (1) yoduro de cobre (375 mg), yoduro de sodio (11,8 g) y N,N'-dimetiletan-1,2-diamina (0,42 ml), y la mezcla permanece toda

la noche a reflujo bajo atmósfera de nitrógeno. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1) para dar etil éster de ácido (2R,4S)-4-[terc-butoxicarbonil-(5-iodopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (21,6 g). MS (m/z): 621 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-[terc-Butoxicarbonil-(5-iodopirimidin-2-il)]-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,0 g), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (35 mg), acetato de potasio (475 mg) y bis(pinacolato)diboro (615 mg) fueron disueltos en dimetilsulfóxido desaereado (8 ml), y la mezcla fue agitada a 80°C durante 18 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados agua y acetato de etilo a los mismos, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (8 ml), y fueron agregados a los mismos una cantidad en exceso de una solución 30% de agua

oxigenada acuosa bajo enfriamiento con hielo, y la mezcla fue agitada durante 6 horas. Se agregan una solución de tiosulfato de sodio acuosa saturada y acetato de etilo a la mezcla bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fueron concentrados bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→19:1) para dar etil éster de ácido (2R,4S)-4-[terc-butoxicarbonil-(5-hidroxipiritnidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,7 g). MS (m/z): 511 $[M+H]^+$

(4) Etil éster de ácido (2R,4S)-4-[terc-butoxicarbonil-(5-hidroxipirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (800 mg) fue disuelto en N,N-dimetilformamida (5 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 72 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 15 minutos, y fueron agregados a los mismos 1-cloro-2-metilsulfaniletano (259 mg), y la mezcla fue agitada a la temperatura ambiente durante 24 horas. Se agregan agua y acetato de etilo a la mezcla de reacción bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida.

El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:7) para dar etil ester de ácido (2R,4S)-4-{terc-butoxicarbonil-[5-(2-metilsulfaniletoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolion-1-carboxílico (200 mg). MS (m/z): 585 $[M+H]^+$

(5) Etil éster de ácido (2R,4S)-4-{terc-Butoxicarbonil-[5-(2-metilsulfonil-etoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en 4N cloruro de hidrógeno en 1,4-dioxano (1,5 ml), y la mezcla fue agitada a la temperatura ambiente durante 17,5 horas. Fue agregado a la solución de reacción una solución 2N de hidróxido de sodio acuosa (3 ml) y dietil éter, y la mezcla fue separada. La capa orgánica fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-2-etil-4[5-(2-metilsulfoniletoxi)pirimidin-2-il]amino-6-trifluoro-metil-3,4-dihidro-2H-quinolin-1-carboxílico (170 mg). MS (m/z):485 $[M+H]^+$

(6) Etil éster de ácido (2R,4S)-2-etil-4-[5-(2-methisulfoniletoxi)pirimidin-2-il]amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (160 mg) fue disuelto en N,N-dimetilformamida (1,5 ml), y a fueron agregados hidruro

de sodio (62,7%; 15 mg) bajo enfriamiento con hielo. La mezcla fue agitada a temperatura ambiente por 30 minutos, y fueron agregados a los mismos bromuro de 3,5-dibromobencilo (141 mg), y la mezcla fue agitada a temperatura ambiente por 19 horas. A la mezcla fue agregado 0,5N ácido clorhídrico y dietil éter bajo enfriamiento con hielo, y fue separada. La capa orgánica fue lavada con solución salina saturada, secada sobre sulfato de magnesio y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-((3,5-dibromobencil)-[5-(2-metilsulfoniletoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (110 mg). MS (m/z): 733 $[M+H]^+$

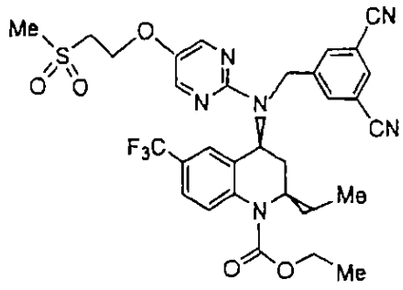
(7) Etil éster de ácido (2R,4S)-4-{(3,5-Dibromobencil)-[5-(2-metilsulfoniletoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) fue disuelto en N,N-dimetilformamida (2 ml), y fueron agregados a éstos cianuro de zinc (35,3 mg) y una cantidad catalítica de tetrakis(trifenilfosfina)paladio, y la mezcla fue agitada a 110°C por 17,5 horas. La solución de reacción fue enfriada a temperatura ambiente, y se agregan a los mismos agua y dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo

presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) dando etil éster de ácido (2R,4S)-4-{(3-bromo-5-cianobencil)-[5-(2-metilsulfonil-etoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (28 mg, MS (m/z): 678/680 $[M+H]^+$), y etil éster de ácido (2R,4S)-4-{(3,5-dicianobencil)-[5-(2-metilsulfonil-etoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (50 mg, MS (m/z): 625. $[M+H]^+$).

(8) Etil éster de ácido (2R,4S)-4-((3-Bromo-5-cianobencil)-[5-(2-metilsulfoniletoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxilico (25 mg) fue disuelto en cloroformo (0,5 ml), y fueron agregados ácido m-cloroperbenzoico (75%, 17 mg), y la mezcla fue agitada a temperatura ambiente por 35 minutos. Se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo a la mezcla, y ésta fue separada. La capa orgánica fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 7:3→4 1:1) dando etil éster de ácido (2R,4S)-4-{(3-bromo-5-cianobencil)-[5-(2-metil-sulfoniletoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (29 mg). MS (m/z):

710/712 $[M+H]^+$

Ejemplo 234



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 233 (8) para dar el compuesto de Ejemplo 234. MS (m/z): 657 $[M+H]^+$

Ejemplo 235

(1) Etil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolir-1-carboxílico (1,0 g) fue disuelto en N,N-dimetilformamida (10 ml), y fueron agregados a los mismos hidruro de sodio (62,7%, 89 mg) bajo enfriamiento con hielo. La mezcla fue agitada en la temperatura ambiente durante 15 minutos, y fueron agregados a los mismos bromuro de 3-ciano-5-trifluorometilbencilo (669 mg), y la mezcla fue agitada a la temperatura ambiente durante 20 horas. Se agregan agua y dietil éter a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R,4S)-4-[(5-

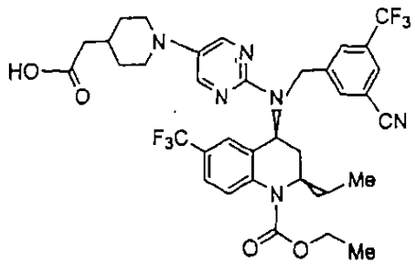
bromopirimidin-2-il)-(3-ciano-5-trifluorometilbencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,08 g). MS (m/z): 656/658 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[(5-bromopirirnidin-2-il)-(3-ciano-5-trifluorometilbencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (250 mg), tris(dibencilidenacetona)dipaladio (35 mg), 2-(di-tertbutilfosfino)difenilo (45 mg), terc-butóxido de sodio (55 mg), y etil éster de ácido piperidin-4-carboxílico (88 µl) fue disuelto en tolueno (2 ml), y la mezcla fue agitada a la temperatura ambiente durante 2,5 horas. La solucion de reacción fue agitada a 80°C durante 15 horas. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución acuosa saturada de carbonato hidrógeno de sodio y agua, una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(4-etoxicarbonilpiperidin-1-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (126,8 mg). MS (m/z): 733 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-((3-Ciano-5-

trifluorometilbencil)-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (120 mg) fue disuelto en etanol (4 ml), y fueron agregados a los mismos 2N solución de hidróxido de sodio acuosa (1 ml), y la mezcla fue agitada a la temperatura ambiente durante 3 horas. A la mezcla se agrega 2N ácido clorhídrico (1 ml) y acetato de etilo, y la mezcla fue separada. La capa orgánica fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 7:3→1:1) y por LC/MS (CAPCEL PAK MG II ("Shiseido Co., Ltd"), agua:metanol = 60:40→metanol, 40 ml/min) para dar etil éster de ácido (2R,4S)-4-{[5-(4-carboxipiperidin-1-il)pirimidin-2-il]-(3-ciano-5-trifluorometilbencil)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (18,6 mg). MS (m/z): 719 $[M+H]^+$

Ejemplo 236



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 235 (2)-(3) para dar el compuesto de Ejemplo 236. MS (m/z): 719 $[M+H]^+$

Ejemplo 237

(1) Etil éster de ácido (2R,4S)-4-[(5-Bromopirimidin-2-il)-(3-ciano-5-trifluorometilbencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (10 g), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (395 mg), acetato de potasio (5,3 g) y bis(pinacolato)diboro (6,8 g) fue disuelto en dimetilsulfóxido desaereado (50 ml), y la mezcla fue agitada a 80°C durante 30 minutos. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (50 ml), y fueron agregados a los mismos una solución 30 % de agua oxigenada acuosa (9 ml) bajo enfriamiento con hielo, y la mezcla fue agitada durante 16 horas. Se agregan una solución de tiosulfato de sodio acuosa saturada y acetato de etilo a la mezcla bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-[(3-ciano-5-trifluorometilbencil)-(5-hidroxipirimidin-2-

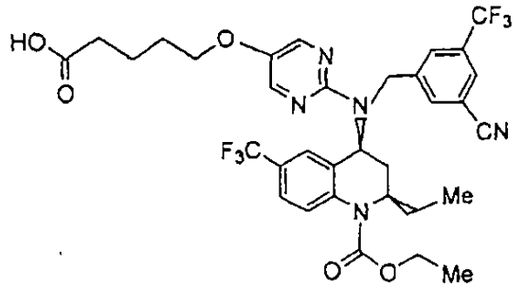
il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin1-carboxílico (7,7 g). MS (m/z): 594 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-[(3-Ciano-5-trifluorometilbencil)-(5-hidroxipirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg) fue disuelto en N,N-dimetilformamida (2,5 ml), y hidruro de sodio (62,7%, 119 mg) fue agregado a los mismos bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. Fue agregadc a la solución de reacciónetil éster de ácido 4-bromobutírico (185 µl), y la mezcla fue agitada a la temperatura ambiente durante 17 horas. A la solución de reacción se agregan agua y acetato de etilo bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con 1N ácido clorhídrico, agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (380 mg). MS (m/z): 708 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{(3-Ciano-5-

trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (370 mg) fue disuelto en una mezcla de etanol (1,5 ml) y tetrahidrofurano (1 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuoso (0,79 ml), y la mezcla fue agitada a la temperatura ambiente durante 3 horas. Fue agregada a la solución de reacción2N ácido clorhídrico (0,8 ml), y la mezcla fue concentrada bajo presión reducida. Al residuo resultante se agrega agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con solución salina saturada, secada sobre sulfato de magnesio, y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3), y LC/MS (CAPCEL PAK MG II ("Shiseido Co. Ltd."), agua:metanol = 50:50→metanol, 40 ml/min) y da etil éster de ácido (2R,4S)-4-{[5-(3-carboxipropoxi)pirimidin-2-il]-(3-ciano-5-trifluorometilbencil)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (167 mg). MS (m/z): 680 [M+H]$^+$

Ejemplo 238



Los compuestos intermedios fueron

tratados de manera similar al Ejemplo 237 (2)-(3) para dar el compuesto de Ejemplo 238. MS (m/z): 694 $[M+H]^+$

Ejemplo 239

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (330 mg) fue disuelto en dimetilsulfóxido (2,5 ml), y fue agregado a los mismos dicloropaladio de [1,1'-bis(difenilfosfino)ferroceno] (11 mg), acetato de potasio (147 mg) y bis(pinacolato)diboro (190 mg), y la mezcla fue agitada a 80°C bajo atmósfera de nitrógeno durante una hora. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos una solución salina saturada y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (3 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (0,3 ml), y a los mismos fue agregada adicionalmente por gotas una solución 30% de agua oxigenada acuosa (3 ml) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante una hora, y fue agregada a los mismos una solución de tiosulfato de sodio acuosa saturada bajo enfriamiento con hielo. Entonces, fueron agregados una solución 10% de ácido cítrico

acuosa y acetato de etilo a la mezcla, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (144 mg). MS (m/z): 599 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (141 mg) fue disuelto en N,N-dimetilformamida (1,5 ml), y fueron agregados a los mismos carbonato de potasio (65 mg) y etil éster de ácido 4-bromobutírico (44 µl). La mezcla fue agitada toda la noche a la temperatura ambiente. Fueron agregados una solución salina saturada y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo =4:1→3:1) para dar etil éster de ácido (2R,4S)-4-({3,5-bis(trifluorometil)bencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-

metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (141 mg).

MS (m/z): 713 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (137 mg) fue disuelto en 1,4-dioxano (1 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (1 ml), y la mezcla fue agitada a 40°C durante una hora. La solución de reacción fue enfriada a la temperatura ambiente, y fue acidificada con una solución 10% de ácido cítrico acuosa. Subsiguientemente, fue agregado acetato de etilo a la mezcla, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 19:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (123 mg). MS (m/z): 685 $[M+H]^+$

Ejemplo 240

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (2,28 g) fue disuelto en tetrahidrofurano (7 ml), y fueron agregados a

los mismos hidruro de sodio (63%, 107 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a 0°C bajo atmósfera de nitrógeno durante 30 minutos. A la mezcla de la reacción fue agregado clorometil éter metílico (0,40 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante una hora. Se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 10:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-metoximetoxi-3,4-dihidro-2H-quinolin-1-carboxílico (1,95 g). MS (m/z): 693/691 $[M+H]^-$

(2) Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-metoximetoxi-3,4-dihidro-2H-quinolin-1-carboxílico (1,93 g) fueron disueltos en dimetilsulfóxido (8 ml), y la mezcla fue desaereada. A la mezcla fue agregado dicloropaladio de [1,1'-bis(difenilfosfino)ferroceno] (61 mg), acetato de potasio (822 mg) y bis(pinacolato)diboro (1,06 g), y la mezcla fue agitada a 80°C bajo atmósfera de nitrógeno durante 45 minutos. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos una

solución salina saturada y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (24 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (14 ml), y además fue agregado por gotas una solución 30% de agua oxigenada acuosa (10 ml) bajo enfriamiento con hielo. La mezcla fue agitada a la misma temperatura durante 30 minutos, y fueron agregados a los mismos a los mismos una solución de tiosulfato de sodio acuosa saturada bajo enfriamiento con hielo, y adicionalmente fue agregada una solución 10% de ácido cítrico acuosa y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo - 4:1→3:1) para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-(5hidroxipirimidin-2-il)}-amino-2-etil-6-metoximetoxi-3,4-dihidro-2H-quinolin-1-carboxílico (1,49 g). MS (m/z): 629 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)benzyl]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-metoximetoxi-3,4-dihidro-2H-quinolin-1-carboxílico (1,49 mg) fue disuelto en N,N-dimetilformamida (7 mL), y

fueron agregados a los mismos hidruro de sodio (62,7%; 109 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 40 minutos. Fue agregado a la solución de reacciónetil éster de ácido 4-bromobutírico (0,52 mL), y la mezcla fue agitada a la temperatura ambiente durante 3 horas. Fue agregada a la solución de reacciónagua y acetato de etilo-hexano = 4:1 bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-metoximetoxi-3,4-dihidro-2H-quinolin-1-carboxílico (1,29 g). MS (m/z): 743 $[M+H]^+$

(4) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirirnidin-2-il]}amino-2-etil-6-methoxymetoxi-3,4-dihidro-2H-quinolin-1-carboxílico (1,29 g) fue disuelto en tetrahidrofurano (5,2 mL), y fueron agregados a los mismos 6N ácido clorhídrico (0,58 mL) bajo enfriamiento con hielo, y la mezcla fue agitada a 50°C durante 2,5 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de

etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→7:3→cloroformo:metanol = 9:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (614 mg, MS (m/z): 699 $[M+H]^+$) y etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (550 mg, MS (m/z): 671 $[M+H]^+$).

(5) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (610 mg), y piridina (424 µl) fue disuelto en cloruro de metileno (4 mL), y fueron agregados a los mismos anhídrido trifluorometansulfónico por gotas (354 µl) bajo enfriamiento con hielo. La solución de reacción fue agitada durante 3,5 horas, y fueron agregados a los mismos una solución saturada de ácido cítrico acuosa y dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre

sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo 9:1→7:3) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometan-sulfoniloxi-3,4-dihidro-2H-quinolin-1-carboxílico (555 mg). MS (m/z): 831 $[M+H]^+$

(6) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometansulfoniloxi-3,4-dihidro-2H-quinolin-1-carboxílico (220 mg), dimetilamina (una solución 2N de tetrahidrofurano, 0,16 mL), acetato de paladio (0,6 mg), 2-(di-terc-butilfosfino)difenilo (3,3 mg) y terc-butóxido de sodio (36 mg) fue disuelto en tolueno (0,52 mL), y la mezcla fue agitada a 80°C durante 21 horas bajo atmósfera de nitrógeno en un recipiente sellado. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→7:3) para dar etil éster de ácido (2R,4S)-4-

{[3,5-bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-6-dimetilamino-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (53 mg). MS (m/z): 726 $[M+H]^+$

(7) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-6-dimetilamino-2-etil-3,4-dihidro-2H- quinolin-1-carboxílico (48 mg) fue disuelto en el etanol (0.3 mL), y fueron agregados a los mismos una 2N solución del hidróxido de sodio acuosa (0.1 mL), y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. Fue agregado a la solución de reacción una solución de ácido cítrico acuosa saturada y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-6-dimetilamino-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (29 mg). MS (m/z): 698 $[M+H]^+$

Ejemplo 241

(1) (2R*,4S*)-4-Benciloxicarbonilamino-(2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (112,8 g) fue

disuelto en metanol (1000 ml) y fueron agregados a los mismos 10% paladio carbono (5,64 g), y la mezcla fue agitada toda la noche a la temperatura ambiente bajo atmósfera de hidrógeno. El carbono paladio fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. Al residuo resultante el hexano normal se agrega, y los cristales precipitados fueron recolectados por filtración y fueron lavados para dar (2R*,4S*)-(4-amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (70,3 g). MS (m/z): 245 $[M+H]^+$

(2) (2R*,4S*)-(4-Amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (70 g) y dicarbonato de di-terc-butilo (68,2 g) fue disuelto en tetrahidrofurano (500 ml), y la mezcla fue agitada toda la noche a la temperatura ambiente. La solución de reacción fue concentrada bajo presión reducida, y fueron agregados a los mismos hexano normal. Los cristales precipitados fueron recolectados por filtración para dar (2R*,4S*)-4-terc-butoxicarbonilamino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (90,7 g). MS (m/z): 345 $[M+H]^+$

(3) (2R*,4S*)-4-terc-Butoxicarbonilamino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (90,58 g) y trietilamina (44 ml) fue disuelto en cloruro de metileno (900 ml), y fueron agregados a los mismos trifosgeno (31,2 g) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante una hora. La solución de reacción fue concentrada bajo presión reducida, y el residuo

resultante y alcohol bencílico (54,4 ml) fueron disueltos en tetrahidrofurano (900 ml), y fueron agregados a los mismos hidruro de sodio (20,2 g) bajo enfriamiento con hielo, y la mezcla fue agitada a la misma temperatura durante 3 horas. Fueron agregdos agua y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo fue cristalizado del isopropil éter para dar bencil éster de ácido (2R*,4S*)-4-terc-butoxicarbonilamino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (104,7 g). MS (m/z): 496 $[M+H_2O]^+$

(4) bencil éster de ácido (2R*,4S*)-4-terc-Butoxicarbonilamino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxilico (104,5 g) fue disuelto en cloroformo (500 ml), y fueron agregados a los mismos 4N ácido clorhídrico en acetato de etilo (500 ml), y la mezcla fue agitada a temperatura ambiente durante 30 minutos. La solución de reacción fue concentrada bajo presión reducida, y al residuo resultante fue agregado isopropil éter, y los cristales precipitados fueron recolectados por filtración y fueron lavados para dar hidrocloruro de bencil éster de ácido (2R*,4S*)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (88.0 g). MS (m/z): 379 $[M-HCl]^+$

(5) Hidrocloruro de bencil éster de ácido (2R*,4S*)-4-amino-

2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (12 g) fue disuelto en una mezcla de una solución 2N de hidróxido de sodio acuosa y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante, y 5-bromo-2-cloropirimidina (16,8 g) y diisopropiletilamina (15 ml) fueron disueltos en 1,4-dioxano (100 ml), y la mezcla fue agitada a 130°C durante 24 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados agua y acetato de etilo a los mismos, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar bencil éster de ácido (2R*,4S*)-4-(5-bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (9,39 g). MS (m/z): 535/537 $[M+H]^+$

(6) Bencil éster de ácido (2R*,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (5 g), tris(dibencilidenacetona)dipaladio (1,71 g), terc-butóxido de sodio (1,35 g), 2-(di-terc-butilfosfino)bifenilo (2,22 g), y tetrahidrooxazina (1,22 ml) fue disuelto en tolueno (50 ml), y la mezcla fue agitada a

50°C bajo atmósfera de nitrógeno durante 5 horas. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 2:1→1:1), luego por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 2:1→1:1) para dar bencil éster de ácido (2R*,4S*)-2-etil-4-[5-(morfolin-4-il)pirimidin-2-il]amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,58 g). MS (m/z): 542 $[M+H]^+$

(7) Bencil éster de ácido (2R*,4S*)-2-etil-4-[5-(morfolin-4-il)pirimidin-2-il]amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,57 g) fue disuelto en N,N-dimetilformamida (20 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 257 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. A la mezcla fue agregado bromuro de 3,5-dibromobencilo (2,64 g) bajo enfriamiento con hielo, y la mezcla fue agitada toda la noche a la temperatura ambiente. Fue agregado a la solución de reacciónagua y acetatc de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una

solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 6:1→4:1) para dar bencil éster de ácido (2R*,4S*)-4-((3,5-dibromobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,41 g). MS (m//z):788/780 $[M+H]^+$

(8) Bencil éster de ácido (2R*,4S*)-4-{(3,5-Dibromobencil)-[5-(morfolin-4-il)pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,38 g), una cantidad catalítica de tetrakis(trifenil-fosfina)paladio y cianuro de zinc (779 mg) fue disuelto en N,N-dimetilformamida (40 ml), y la mezcla fue agitada a 110°C bajo atmósfera de nitrógeno durante 4 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→2:1) para dar bencil éster de ácido (2R*,4S*)-4-{(3,5-dicianobencil)-[5-(morfolin-4-il)-pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico (1,66 g). MS (m/z): 682 $[M+H]^+$

Ejemplo 242

(1) Bencil éster de ácido (2R*,4S*)-4-{(3,5-Dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,6 g) fue disuelto en una mezcla de metanol (10 ml) y tetrahidrofurano (10 ml), y fueron agregados a los mismos una cantidad catalítica de 10% paladio carbono, y la mezcla fue agitada a la temperatura ambiente bajo atmósfera de hidrógeno durante una hora. El catalizador fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 2:1→1:1) para dar (2R*,4S*)-4-((3,5-dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (1,07 g). MS (m/z): 548 $[M+H]^+$

(2) (2R*,4S*)-4-{(3,5-Dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}-amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (150 mg) y trietilamina (76 µl) fue disuelto en diclorometano (1,5 ml), y fueron agregados a los mismos trifosgeno (33 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 3 horas. Fue agregado a la solución de reacciónagua y acetato de etilo, y la capa orgánica fue lavada con una solución salina

saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante y etilén glicol (1 ml) fueron disueltos en tetrahidrofurano (2,5 ml), y fueron agregados a los mismos trietilamina (400 µl) y una cantidad catalítica de 4-dimetilaminopiridina bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante una hora. Fue agregado a la solución de reacciónagua y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 1:2→1:4) para dar 2-hidroxiletil éster de ácido (2R*,4S*)-4-{(3,5-dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (156 mg). MS (m/z): 636 $[M+H]^+$

Ejemplo 243

(2R*,4S*)-4-{(3,5-Dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (200 mg) y isocianato de 2-bromoetilo (200 µl) fue disuelto en tolueno (2 ml), y la mezcla fue agitada a 90°C durante 8 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La

capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en el N N,N-dimetilformamida (2 ml), y fueron agregados a los mismos hidruro de sodio (62,7%, 100 mg) bajo enfriamiento con hielo. La mezcla fue agitada a 90°C durante 30 minutos. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos el agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 1:4→0:1) para dar (2R*,4S*)-4-{(3,5-dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-1-(4,5-dihidrooxazol-2-il)-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (97 mg). MS (m/z): 617 $[M+H]^+$

Ejemplo 244

(1) 4-Aminobenzotrifluoruro (100 g) y benzotriazol (74 g) fue disuelto en tolueno (1200 ml), y fueron agregados a los mismos propionaldehído por gotas (49,3 ml) bajo enfriamiento con hielo, y la solución de reacción fue agitada toda la noche a la temperatura ambiente. El heptano (600 ml) fue agregado, y la mezcla fue agitada adicionalmente durante 30 minutos. El precipitado fue recolectado por filtración, y fue

lavado con heptano para dar {[1-(benzotriazol-1-il)propil]-(4-trifuorometilfenil)}amina (140,9 g).

(2) {[1-(Benzotriazol-1-il)propil]-(4-trifluorometilfenil)}amina (140 g), 1-fenuletil éster de ácido (S)-vinilcarbámico (83,5 g) y ácido p-toluensulfónico (1,66 g) fueron disueltos en tolueno (1500 ml), y la mezcla fue agitada a 80°C durante 3 horas. A la mezcla se agregan una solución 2N de hidróxido de sodio acuosa y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue recristalizado del isopropil éter para dar (2R,4S)-4-((S)-1-feniletoxicarbonilamino)-6-trifluorometil-1,2,3,4-tetrahidroquinolina (36,4 g). S (m/z): 393 $[M+H]^+$

(3) (2R,4S)-(4-((S)-1-Feniletoxicarbonilamino)-6-trifluorometil-1,2,3,4-tetrahidroquinolina (2,25 g) fue disuelto en una mezcla de metanol (15 ml) y tetrahidrofurano (5 ml), y fueron agregados a los mismos 10% paladio carbono (200 mg). La mezcla fue agitada a la temperatura ambiente bajo atmósfera de hidrógeno durante 4 horas. El paladio carbono fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (15 ml), y fueron agregados a los mismos dicarbonato de di-terc-butilo (1,25 g), y la mezcla fue agitada toda la noche a la temperatura ambiente.

La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→7:3) para dar (2R,4S)-4-4-terc-butoxicarbonilamino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (2,0 g). MS (m/z): 345 $[M+H]^+$

(4) (2R,4S)-4-(terc-Butoxicarbonilamino)-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (2,0 g) y trietilamina (972 µl) fue disuelto en cloruro de metileno (20 ml), y fueron agregados a los mismos trifosgeno (690 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante una hora. Se agregan acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo y alcohol bencílico (1,2 ml) fueron disueltos en tetrahidrofurano (30 ml), y a los mismos fuer agregado hidruro de sodio (446 mg) bajo enfriamiento con hielo, y la mezcla fue agitada toda la noche a la temperatura ambiente. Fueron agregados agua y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo

fue disuelto en cloroformo (10 ml), y fueron agregacos a los mismos 4N cloruro de hidrógeno en acetato de etilo (10 ml), y la mezcla fue agitada a la temperatura ambiente durante una hora. A la solución de reacción fueron agregados acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida para dar bencil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,73 g). MS (m/z): 379: $[M+H]^+$

(5) Bencil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,73 g) y 5-bromo-2-cloropirimidina (2,21 g) fue disuelto en 1,4-dioxano (20 ml), y fueron agregados a los mismos N,N-diisopropiletilamina (1,99 ml), y la mezcla fue dejada toda la noche a reflujo. Fue agregado a la solución de reacción una solución salina saturada y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→3:1) para dar bencil éster de ácido (2R,4S)-4-(5-bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,02 g). MS (m/z): 535/537

$[M+H]^+$

(6) Bencil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,0 g) fue disuelto en N,N-dimetilformamida (15 ml), y fueron agregados a los mismos hidruro de sodio (177 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la misma temperatura durante 20 minutos, y fueron agregados a los mismos bromuro de 3,5-bis(trifluorometil)bencilo (1,03 ml), y la mezcla fue agitada a la misma temperatura durante una hora. Fue agregado a la solución de reacciónacetato de etilo y agua, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice. (hexano:acetato de etilo = 95:5→3:1) para dar bencil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,19 g). MS (m/z): 761/763 $[M+H]^+$

(7) Bencil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,15 g), etil éster de ácido isonipecótico (634 µl), terc-butóxido de sodio (407 mg) y 2-(di-terc-butilfosfino)bifenilo

(337 mg) fue disuelto en tolueno (20 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (258 mg), y la mezcla fue agitada toda la noche a la temperatura ambiente bajo atmósfera de nitrógeno. Fue agregado a la solución de reacción acetato de etilo y agua, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→4:1) para dar bencil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,30 g). MS (m/z): 838 $[M+H]^+$

(8) Bencil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,28 g) fue disuelto en etanol (15 ml), y fueron agregados a los mismos 10% paladio carbono (200 mg), y la mezcla fue agitada a la temperatura ambiente bajo atmósfera de hidrógeno durante 1,5 hora. El paladio-carbono

fue eliminado por filtración, y el filtrado obtenido fue concentrado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→4:1) para dar (2R, 4S)-4-{[3,5-

bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidro-quinolina (1,02 g). MS (m/z): 704 $[M+H]^+$

(9) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (250 mg) y trietilamina (60 µl) fue disuelto en cloruro de metileno (3 ml), y fueron agregados a los mismos trifosgeno (42 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 30 minutos, y fueron agregados a los mismos acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue disuelto en tetrahidrofurano (1 ml), y fueron agregados a los mismos un 2-fluoroetanol (0,5 ml), trietilamina (0,5 ml) y 4-dimetilaminopiridina (10 mg), y la mezcla fue agitada toda la noche a la temperatura ambiente. A la mezcla se agregan agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→4:1) para dar 2-fluoroetil éster de ácido (2R,4S)-4-

{[3,5bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4dihidro-2H-quinolin-1-carboxílico (215 g). MS (m/z): 794 $[M+H]^+$

Ejemplos 245-247

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 244 (9) para dar los compuestos como los enumerados en la Tabla 31.

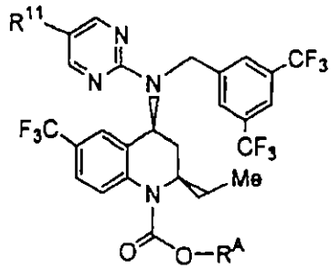
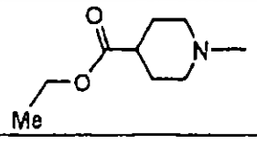
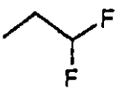
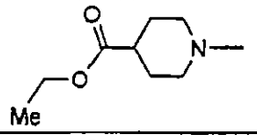
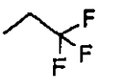
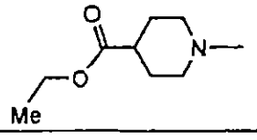
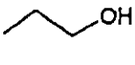


Tabla 31

Ej. No.	R^{11}	R^A	Propiedades fisicas, etc.
245			MS (m/z): 812 $[M+H]^+$
246			MS (m/z): 830 $[M+H]^+$
247			MS (m/z): 792 $[M+H]^+$

Ejemplo 248

(1) Bencil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (4,87 g), [1,1'-bis(difenilfosfino)ferroceno]-dicloropaladio

(140 mg), acetato de potasio (1,88 g), y bis(pinacolato)diboro (3,25 g) fue disuelto en dimetilsulfóxido (45 ml), y la mezcla fue agitada a 80°C bajo atmósfera de nitrógeno durante una hora. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (50 ml), y fueron agregados a los mismos por gotas una solución 30% de agua oxigenada acuosa (10 ml) bajo enfriamiento con hielo. Una hora después de esto, una solución de tiosulfato de sodio acuosa saturada fue agregada a la mezcla de reacción bajo enfriamiento con hielo, y la cantidad en exceso de agua oxigenada fue consumida. Fueron agregados agua y acetato de etilo a la mezcla de reacción, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→4:1) para dar bencil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,73 g). MS (m/z): 699 $[M+H]^+$

(2) Bencil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,71 g) y etil éster de ácido 4-bromobutírico (617 µl) fue disuelto en N,N-dimetilformamida (10 ml), y fueron agregados a los mismos carbonato de potasio (644 mg), y la mezcla fue agitada toda la noche a 45°C. Se agregan acetato de etilo y una solución salina saturada a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→4:1) para dar bencil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,78 g). MS (m/z): 813 $[M+H]^+$

(3) Bencil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,77 g) fue disuelto en etanol (30 ml), y fueron agregados a los mismos 10% paladio carbono (500 mg), y la mezcla fue agitada a la temperatura ambiente bajo atmósfera de hidrógeno durante

3 horas. El paladio carbono fue eliminado por filtración, y el filtrado obtenido fue concentrado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo =95:5→4:1) para dar (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (2,23 g). MS (m/z): 679 $[M+H]^+$

(4) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (319 mg) y trietilamina (79 µl) fue disuelto en cloruro de metileno (2 ml), y fueron agregados a los mismos trifosgeno (56 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. A la mezcla se agregan acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue disuelto en el tetrahidrofurano (1 ml), y fueron agregados a los mismos 2-fluoroetanol (0,5 ml), trietilamina (0,5 ml) y 4-dimetilaminopiridina (10 mg), y la mezcla fue agitada toda la noche a la temperatura ambiente. Se agregan agua y acetato de

etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de silice (hexano:acetato de etilo = 95:5→44:1) para dar 2-fluoroetil éster de ácido (2R,4S)-4-([3,5bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (173 mg). MS (m/z): 769 $[M+H]^+$

Ejemplos 249-253

Los compuestos de comienzo correspondientes fueron tratados en una manera similar al Ejemplo 248 (4) para dar los compuestos como los enumerados en la Tabla 32.

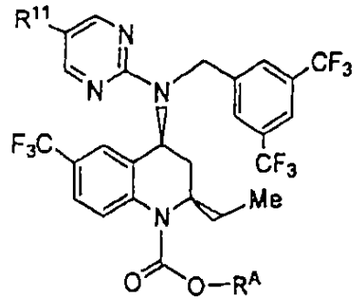
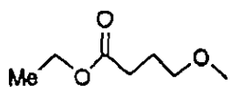
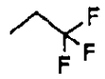
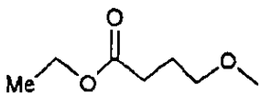
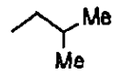
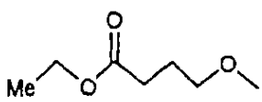
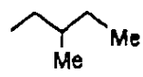
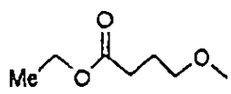
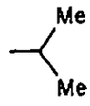
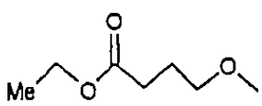
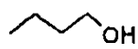


Tabla 32

Ej. No.	R^{11}	R^A	Propiedades físicas, etc.
249			MS (m/z): 805 $[M+H]^+$
250			MS (m/z): 779 $[M+H]^+$
251			MS (m/z): 793 $[M+H]^+$
252			MS (m/z): 765 $[M+H]^+$
253			MS (m/z): 781 $[M+H]^+$

Ejemplos 254-261

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 177 (3) para dar los compuestos como los enumerados en la Tabla 33.

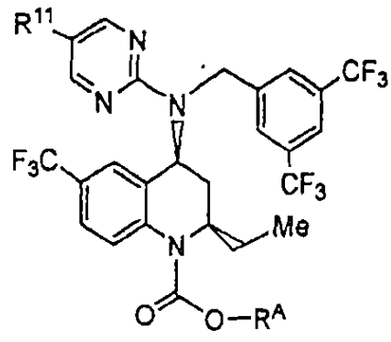
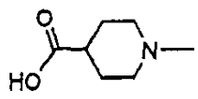
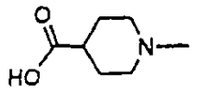
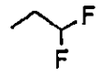
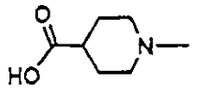
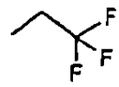
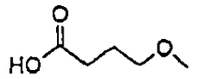
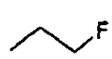
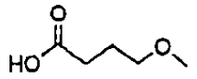
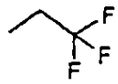
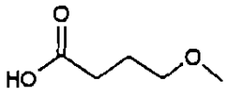
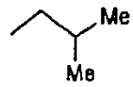
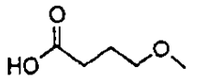
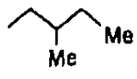
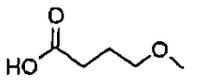
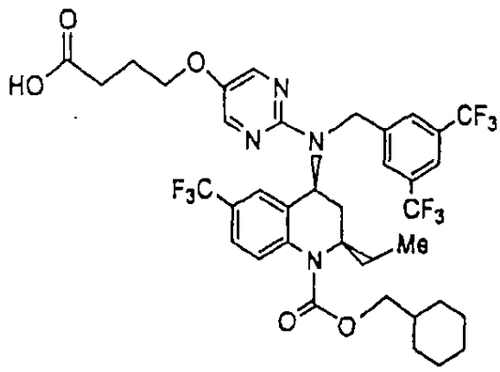


Tabla 33

Ej. No.	R^{11}	R^A	Propiedades físicas, etc.
254			MS (m/z): 766 $[M+H]^+$
255			MS (m/z): 784 $[M+H]^+$
256			MS (m/z): 802 $[M+H]^+$
257			MS (m/z): 741 $[M+H]^+$
258			MS (m/z): 777 $[M+H]^+$
259			MS (m/z): 751 $[M+H]^+$
260			MS (m/z): 765 $[M+H]^+$
261			MS (m/z): 737 $[M+H]^+$

Ejemplo 262



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 248 (4) y Ejemplo 177 (3) para dar el compuesto de Ejemplo 262. MS (m/z): 791 $[M+H]^+$

Ejemplo 263

2-Hidroxiletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirirnidin-2-il]}amino-2etil-6-trifiuorometil-3,4-dihidro-2H-quinolin-1-carboxílico (215 mg) fue disuelto en tetrahidrofurano (2 ml), y fueron agregados a los mismos una solución 1N de hidróxido de sodio acuosa (2 ml), y la mezcla fue agitada a 50°C durante 2 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos acetato de etilo y 1N ácido clorhídrico, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:4) para dar 2-hidroxiletil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (47 mg, MS (m/z): 764 $[M+H]^+$) y (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (90 mg, MS (m/z):

676 $[M+H]^+$).

Ejemplo 264

3-Hidroxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (165 mg) fue disuelto en etanol (2 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (317 µl), y la mezcla fue agitada a la temperatura ambiente durante 3 horas. A la mezcla se agregan acetato de etilo y 1N ácido clorhídrico, y la mezcla fue separada. La capa organica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de silicio de capa delgada (hexano:acetato de etilo = 1:1) para dar 3-hidroxipropil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (37 mg, MS (m/z): 753 $[M+H]^+$) y 3-acetoxipropil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihydi-o-2H-quinolin-1-carboxílico (116 equipo, MS (m/z): 795 $[M+H]^+$).

Ejemplo 265

(1) Bencil éster de ácido (2R,4S)-4-(5-Bromopirimidin-2-

il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (7,9 g) fue disuelto en N,N-dimetilformamida (35 ml), y fueron agregados a los mismos hidruro de sodio (737 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la misma temperatura durante 20 minutos, y fueron agregados a los mismos 3-bromometil-5-cianobenzotrifluoruro (5,85 g), y la mezcla fue agitada a la misma temperatura durante una hora. Fue agregado a la solución de reacciónacetato de etilo y una solución salina saturada, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→3:1) para dar bencilo éster de ácido (2R,4S)-4-[(5-bromopirimidin-2-il)-(3-ciano-5-trifluorometilbencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (4,84 g). MS (m/z): 718/720 $[M+H]^+$

(2) Bencil éster de ácido (2R,4S)-4-[(5-Bromopirimidin-2-il)-(3-ciano-5-trifluorometilbencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (4,82 g), [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (147 mg), y acetato de potasio (1,98 g), y bis(pinacolato)diboro (2,56 g) fueron disueltos en dimetilsulfóxido (30 ml), y la mezcla fue agitada a 80°C bajo atmósfera de nitrógeno durante una hora. La solución de reacción fue enfriada a la temperatura

ambiente, y fueron agregados a los mismos acetato de etilo y una solución salina saturada, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (80 ml), y fueron agregados a los mismos por gotas una solución 30% de agua oxigenada acuosa (50 ml) bajo enfriamiento con hielo. Una hora después de esto, una solución de tiosulfato de sodio acuosa saturada fue agregada a la mezcla bajo enfriamiento con hielo, y una cantidad en exceso de agua oxigenada fue consumida. A la mezcla se agrega acetato de etilo y agua, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar bencil éster de ácido (2R,4S)-4-[(3-ciano-5-trifluorometilbencil)-(5-hidroxipirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quirolin-1-carboxílico (2,47 g). MS (m/z): 656 $[M+H]^+$

(3) Bencil éster de ácido (2R,4S)-4-[(3-Ciano-5-trifluorometilbencil)-(5-hidroxipirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,46 g) y etil éster de ácido 4-bromobutírico (597 µl) fue

disuelto en N,N-dimetilformamida (20 ml), y fueron agregados a los mismos carbonato de potasio (622 mg), y la mezcla fue agitada a 50°C durante 5 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos acetato de etilo y agua, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo 95:5→3:2) para dar bencil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,29 g).
MS (m/z): 770 $[M+H]^+$

(4) Bencil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,28 g) fue disuelto en etanol (25 ml), y fueron agregados a los mismos 10% paladio carbono (500 mg), y la mezcla fue agitada a la temperatura ambiente bajo atmósfera de hidrógeno durante una hora. El paladio carbono fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→3:1) para dar (2R,4S)-4-{(3-ciano-5-

trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (1,77 g). MS (m/z): 636 $[M+H]^+$

(5) (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (500 mg) y trietilamina (132 µl) fue disuelto en cloruro de metileno (5 ml), y fueron agregados a los mismos el trifosgeno (93 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante una hora. A la mezcla se agregan acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue disuelto en el tetrahidrofurano (5 ml), y fueron agregados a los mismos 2,2,2-trifluoroethanol (0,5 ml) y trietilamina (0,5 ml), y la mezcla fue agitada toda la noche a la temperatura ambiente. A la mezcla se agregan agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesic y fue concentrada bajo presión reducida. El residuo es purificado por la cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→7:3) para dar 2,2,2-

trifluoroetil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinclin-1-carboxílico (457 mg). MS (m/z): 762 $[M+H]^+$

(6) 2,2,2-trifluoroetil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (436 mg) fue disuelto en etanol (2 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (859 µl), y la mezcla fue agitada a la temperatura ambiente durante una hora. A la mezcla se agregan acetato de etilo y una solución de ácido cítrico acuosa saturada, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo =9:1→3:2) y LC/MS ("CAPCEL PAK MG II ("Shiseido Co. Ltd."), agua:metanol = 60:40→metanol, 40 ml/min) para dar 2,2,2-trifluoroetil éster de ácido (2R,4S)-4-{[5-(3-carboxipropoxi)pirimidin-2-il]-(3-ciano-5-trifluorometilbencil)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (82 mg, MS (m/z): 734 [M+H]+) y 2,2,2-trifluoroetil éster de ácido (2R,4S)-4-{(3-carboxi-5-trifluorometilbencil)-[5-(3-

etoxicarbonilpropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (70 mg, MS (m/z): 781 $[M+H]^+$).

Ejemplo 266

(1) Bencil éster de ácido (2R*,4S*)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (13 g) fue disuelto en N,N-dimetilformamida (100 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 1,2 g) bajo enfriamiento con hielo y subsiguientemente bromuro de 3,5-bis(trifluorometil)bencilo (6,68 ml), y la mezcla fue agitada a la temperatura ambiente durante 17,5 horas. Se agregan agua y dietil éter a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de silice (hexano:acetato de etilo = 9:1) para dar bencil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il))amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (20,6 g). MS (m/z): 761/763 $[M+H]^+$

(2) bencil éster de ácido (2R*,4S*)-4-([3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il))amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (18,3 g), tris(dibencilidenacetona)dipaladio (439,5 mg), 2-

(di-terc-butilfosfino)difenilo (572,3 mg), terc-butóxido de sodio (3,46 g), y tetrahidrooxazina (3,14 ml) fue disuelto en tolueno (120 ml), y la mezcla fue agitada a la temperatura ambiente durante una hora. La solución de reacción fue agitada a 80°C durante una hora. Fue agregado a la solución de reacciónge1 de NH-sílice, y la mezcla fue filtra. Al filtrado se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→6:1) para dar (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-i]}amino-2-bencil éster de ácido etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (11,2 g). MS (m/z): 768 $[M+H]^+$

(3) (2R*,4S*)-4-([3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il])amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina bencil éster de ácido 1-carboxílico (11,2 g) fue disuelto en una mezcla de tetrahidrofurano (90 ml) y metanol (30 ml), y fueron agregados a los mismos 10 paladio carbono (5 g), y la mezcla fue agitada bajo el atmósfera de hidrógeno durante 21 horas. El catalizador eliminado por filtración, y el filtrado fue concentrado bajo

presión reducida. El residuo es purificado por la cromatografía en columna de gel de NH-sílice (el cloroformo) y cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirirriidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinoline (8,9 g). MS (m/z): 634 $[M+H]^+$

(4) (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluoromethyl1,2,3,4-tetrahidroquinolina (300 mg) fue disuelto en cloruro de metileno (2,5 ml), y fueron agregados a los mismos trietilamina (197 µl) y trifosgeno (147 mg), y la mezcla fue agitada a la temperatura ambiente durante 2 horas y 40 minutos. La solución de reacción fue concentrada, y el residuo fue disuelto en tetrahidrofurano (2,5 ml), y fueron agregados a los mismos trietilamina (0,6 ml), una cantidad catalítica de 4-(dimetilamino)piridina, y pentano-1,5-diol (0,6 ml), y la mezcla fue agitada a la temperatura ambiente durante 14 horas. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→1:1) para dar ácido 5-

hidroxipentil éster (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (261 mg). MS (m/z): 764 $[M+H]^+$

Ejemplo 267

(1) (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluororrietil-1,2,3,4-tetrahidro-quinolina (500 mg) fue disuelto en cloruro de metileno (3 ml), y fueron agregados a los mismos trietilamina (212 µl) y trifosgeno (150 mg), y la mezcla fue agitada a la temperatura ambiente durante 2 horas. La solución de reacción fue concentrada bajo presión reducida, y fueron agregados a los mismos una solución saturada de carbonato hidrógeno de sodio acuosa y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (5 ml), y fueron agregados a los mismos 4-hidroximetil-1-terc-butoxicarbonilpiperidina (204 mg) e hidruro de sodio (30 mg), y la mezcla fue agitada a la temperatura ambiente durante 3 días. A la mezcla se agregan una solución salina saturada y acetato de etilo, y la mezcla fue separada. La capa orgánica fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por

cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→3:2) para dar (1-terc-butoxicarbonilpiperidin-4-il)metil éster de ácido (2R*,4S*)-4-{[3,5-bis(tritluorometil)bencil]-[5-(morfolin4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (282 mg). MS (m/z): 875 [M+H]•

(2) (1-terc-butoxicarbonilpiperidin-4-il)metil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirirnidin-2-il]}amino-2-etil-6-trifuorometil-3,4-dihidro-2H-quinolin-1-carboxílico (282 mg) fue disuelto en el acetato de etilo (3 ml), y fueron agregados a los mismos 4N cloruro de hidrógeno en acetato de etilo = (1 ml), y la mezcla fue agitada toda la noche a la temperatura ambiente. A la mezcla se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo: metanol = 9:1→7:3) para dar piperidin-4-ilmetil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (38 mg). MS (m/z): 775 $[M+H]^+$

Ejemplo 268

(1) Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (13,7 g) fue disuelto en cloruro del metileno (100 ml), y la mezcla se refresca a -70°C, y fueron agregados a los mismos tribromuro de boro por gotas (1M solución de cloruro de metileno, 41,4 ml) bajo atmósfera de nitrógeno. La solución de reacción fue calentada gradualmente a la temperatura ambiente con agitación durante un período de 1,5 hora. La mezcla fue agitada además a la temperatura ambiente durante 21 horas. Fue agregado a la solución de reacción una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 19:1→1:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (3,1 g). MS (m/z): 647/649 $[M+H]^+$

(2) Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)} amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (3,1 g), imidazol (0,98 g), y cloruro de terc-butildimetilsililo fue

disuelto en N,N-dimetilformamida (25 ml), y la mezcla fue agitada a la temperatura ambiente durante 15,5 horas. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil}bencil]-(5-bromopirimidin-2-il)}amino-6-(terc-butildimetilsilaniloxi)2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (3,88 g). MS (m/z): 761/763 $[M+H]^+$

(3) Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-6-(terc-butildimetilsilaniloxi)-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (3,85 g), [1,1'-bis(difenil-fosfino)ferroceno]-dicloropaladio (111 mg), acetato de potasio (1,5 g) y bis(pinacolato)diboro (1,9 g) fueron disueltos en dimetil sulfóxido desaereado (50 ml), y la mezcla fue agitada a 80°C durante 30 minutos. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue

disuelto en tetrahidrofurano (15 ml), y fueron agregados a los mismos una solución acuosa 30% del peróxido de hidrógeno (3,4 ml) bajo enfriamiento con hielo, y la mezcla fue agitada por una hora y 45 minutos. Fueron agregadas una solución acuosa saturada de tiosulfato de sodio y acetato de etilo a la mezcla bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por la cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (2,0 g). MS (m/z): 585 $[M+H]^+$

(4) Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-hidroxi-3,4-dihidro-2H-quinolin-1-carboxílico (2.0 g) fue disuelto en N,N-dimetilformamida (10 ml), y a los mismos fueron agregados hidruro de sodio (62,7%; 144 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. Fue agregado a la solución de reacciónetil éster de ácido 4-bromobutírico (502 µl), y la mezcla fue agitada a la temperatura ambiente durante 6 horas. Fue agregada a la solución de reacciónagua y

acetato de etilo bajo enfriamiento con hielo, y la capa orgánica fue lavada con una solución salina saturada, secada sobre sulfato de magnesio y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→1:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-6-(3-etoxicarbonilpropoxi)-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (578 mg). MS (m/z): 813 $[M+H]^+$

(5) Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-etoxicarbonilpropoxi)pirimidin-2-il]}amino-6-(3-etoxicarbonilpropoxi)-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) fue disuelto en etanol (1,75 ml), y fueron agregados a los mismos una solución acuosa 2N hidróxido de sodio (0,55 ml), y la mezcla fue agitada a la temperatura ambiente por 3 horas. A la mezcla se agrega un 2N ácido clorhídrico (0,55 ml) y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante es purificado por la cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar etil éster de ácido

(2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)-pirimidin-2-il]}amino-6-(3-carboxipropoxi)-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (207 mg). MS (m/z): 757 $[M+H]^+$

Ejemplo 269

(1) (2R*,4S*)-4-([3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (1,0 g), y trietilamina (424 µl) fue disuelto en cloruro de metileno (6,5 ml), y fueron agregados a los mismos trifosgeno (300 mg) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 2 horas. La solución de reacción fue concentrada bajo presión reducida, y al residuo fue agregado una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, secada sobre sulfato de magnesio y concentrada bajo presión reducida. El residuo resultante y bromoetanol (1 ml) fue disuelto en tetrahidrofurano (10 ml), y a los mismos fue agregado trietilamina (460 µl) y una cantidad catalitica de 4-dimetilaminopiridina, y la mezcla fue agitada a la temperatura ambiente por 3 días. Fue agregada a la solución de reacción una solución salina saturada y acetato de etilo, y la mezcla fue separada. La capa orgánica fue secada sobre

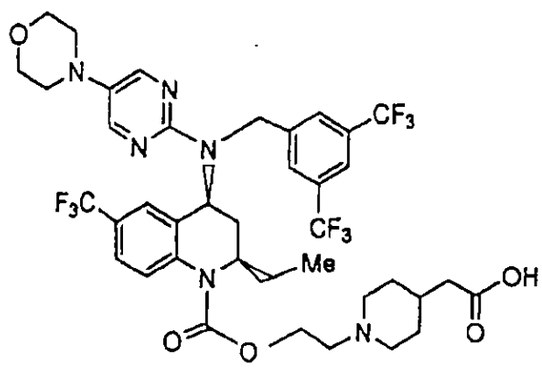
sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar 2-bromoetil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinclin-1-carboxílico (1,51 g) como un producto en bruto. MS (m/z): 784/786 $[M+H]^+$

(2) El 2-bromoetil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (750 mg) fue disuelto en N,N-dimetilformamida (5 ml), y fueron agregados a los mismos etil éster de ácido piperidin-4-carboxílico (442 µl) y carbonato de potasio (400 mg), y la mezcla fue agitada toda la noche a 60°C. A la solución de reacción le fue agregada agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 7:3→1:1) para dar 2-(4-etoxicarbonilpiperidin-1-il)etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[S-(morfolin-4-il)pirimidin-2il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico (439 mg). MS (m/z): 861 $[M+H]^+$

(3) 2-(4-etoxicarbonilpiperidin-1-il)etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (439 mg) fue disuelto en etanol (8 ml), y fueron agregados a los mismos por gotas 1N solución de hidróxido de sodio acuosa (4 ml), y la mezcla fue agitada a la temperatura ambiente toda la noche. A la solución de reacción fueron agregados 1N de ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar 2-(4-carboxipiperidin-1-il)etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (307 mg). MS (m/z): 833 $[M+H]^+$

Ejemplo 270



Los compuestos de comienzo correspondientes fueron tratados en una manera similar al Ejemplo 269 para dar el compuesto de Ejemplo 270. MS (m/z): 847 $[M+H]^+$

Ejemplo 271

(1) 5-hidroxipentil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en diclorometano (1,5 ml), y fueron agregados a los mismos [1,1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona] (124 mg), y la mezcla fue agitada en la temperatura ambiente durante 30 minutos. Fue agregada a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue concentrada bajo presión reducida, y el residuo resultante fue purificado por la cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→3:2) para dar 4-formilbutil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (104 mg). MS (m/z): 762 $[M+H]^+$

(2) 4-Formilbutil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) fue disuelto en una mezcla de terc-butanol:agua (4:1, 1,5 ml), y fueron agregados a los mismos

2-metil-2-butileno (77 µl), dihidrato de dihidrogenfosfato de sodio (28 mg) y clorito de sodio (47 mg) a la temperatura ambiente, y la mezcla fue agitada durante 1,5 hora. Fue agregado a la solución de reacción1N ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→19:1) para dar 4-carboxibutil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (43,1 mg). MS (m/z): 778 $[M+H]^+$

Ejemplo 272

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3 g) fue disuelto en tetrahidrofurano:etanol (1:1, 30 ml), y fueron agregados a los mismos hidróxido de sodio (858 mg), y la mezcla fue agitada a 80°C durante 9 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos 1N ácido clorhídrico (22 ml), y la mezcla fue concentrada bajo presión reducida. Al residuo resultante fueron agregados agua y dietil éter, y la mezcla

fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→3:1) y cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 9:1→3:1) para dar (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-dihidroquinolina (1,79 g). MS (m/z): 626/628[M+H]$^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoroinetil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (800 mg) fue disuelto en diclorometano (6 ml), y fueron agregados a los mismos trietilamina (444 µl) y trifosgeno (303 mg), y la mezcla fue agitada a la temperatura ambiente durante 5 horas. La solución de reacción fue concentrada bajo presión reducida, y los materiales insolubles fueron eliminados por filtración con dietil éter. El filtrado fue concentrado bajo presión reducida, y el residuo resultante fue disuelto en tetrahidrofurano (6 ml), y a la mezcla fue agregados 60% hidruro de sodio (92 mg) y 1,5-pentandiol (400 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 30 minutos, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con 1N ácido

clorhídrico, agua, y una solución salina saturada, y fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar 5-hidroxipentil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil](5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (643.6 mg). MS (m/z): 757/759 $[M+H]^+$

(3) 5-hidroxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (640 mg) fue disuelto en la acetona (5 ml), y fueron agregados a los mismos 1,94M de reactivo Jones (1,38 ml) bajo enfriamiento con hielo, y la mezcla fue agitada durante 1,5 hora. A la solución de reacción fueron agregados hidrogenesulfito de sodio y agua bajo enfriamiento con hielo, y la mezcla fue concentrada bajo presión reducida. Al residuo resultante fue agregado 1N ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar 4-carboxibutil éster de ácido (2R,4S)-4-{[3,5-

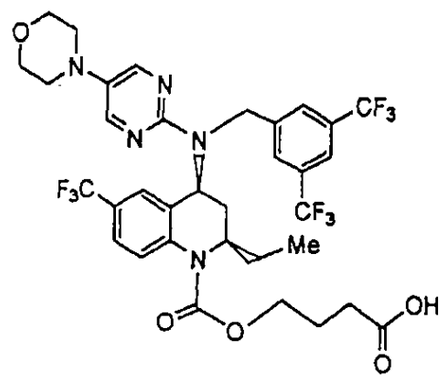
bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (517,2 mg). MS (m/z): 771/773 $[M+H]^+$

(4) 4-carboxibutil éster de ácido (2R,4S)-4-{(3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (510 mg) fue disuelto en tetrahidrofurano:metanol (5:1, 6 ml), y fueron agregados a los mismos una solución 2M de (trimetilsilil)diazometano en hexano (0,86 ml) bajo enfriamiento con hielo, y la mezcla fue agitada durante una hora y 40 minutos. La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (466 mg). MS (m/z): 785/787 $[M+H]^+$

(5) 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (460 mg) fue disuelto en tolueno (3,5 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (54 mg), 2-(di-terc-butilfosfino)bifenilo (36 mg), terc-butóxido de sodio (112 mg) y tetrahidrooxazina (102 µl), y la mezcla fue

agitada a la temperatura ambiente por 3 horas. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución acuosa saturada de ácido cítrico, agua, y una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por la cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar 4-carboxibutil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (72,5 mg). MS (m/z): 778 $[M+H]^+$

Ejemplo 273



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 272 para dar el compuesto del Ejemplo 273. MS (m/z): 764 $M+H]^+$

Ejemplo 274

(1) 6-metoxicarbonilhexil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-

etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (574 mg) que se obtiene tratando los compuestos de comienzo correspondientes de una manera similar al Ejemplo 272 (1)-(4), fue disuelto en tolueno (4,5 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (0) (65 mg), 2-(di-tertbutilfosfino)bifenilo (84 mg), tetrahidrooxazina (123 µl) y terc-butóxido de sodio (136 mg), y la mezcla fue agitada en la temperatura ambiente bajo atmósfera de nitrógeno durante 5 horas. La mezcla de reacción fue neutralizada con una solución 10% de ácido cítrico acuosa, y fueron agregados a los mismos una solución salina saturada, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→2:1→cloroformo:metanol = 100:1→19:1) para dar 6-metoxicarbonilhexil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (119 mg). MS (m/z): 820[M+H]$^+$

(2) 6-metoxicarbonilhexil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico (116 mg) fue disuelto en una mezcla de tetrahidrofurano (2 ml) y metanol (1 ml), y a la mezcla fue agregada una solución 1M de hidróxido de sodio acuosa (1 ml), y la mezcla fue agitada a la temperatura ambiente durante una hora. La mezcla de reacción fue acidificada con una solución 10% de ácido cítrico acuosa, y fueron agregados a los mismos una solución salina saturada, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar 6-carboxihexil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (85 mg). MS (m/z): 806 $[M+H]^+$

Ejemplo 275

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,01 g) fue disuelto en cloroformo (20 ml), y fueron agregados a los mismos yoduro de trimetilsililo (5 g), y la mezcla fue agitada toda la noche bajo atmósfera de nitrógeno a 55°C. A la mezcla de reacción fue agregada una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla

fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 9:1) para dar (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (2,22 g). MS (m/z):626/628 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (500 mg) fue disuelto en diclorometano (4 ml), y fueron agregados a los mismos trietilamina (556 µl) y trifosgeno (380 mg), y la mezcla fue agitada a la temperatura ambiente durante 1,5 hora. La solución de reacción fue concentrada bajo presión reducida, y fueron agregados a los mismos dietil éter, y los materiales insolubles fueron eliminados por filtración. El filtrado fue concentrado bajo presión reducida, y el residuo resultante fue disuelto en tetrahidrofurano (4 ml), y fueron agregados a los mismos etil éster de ácido 6-hidroxihexanonico (156 µl) y trietilamina (167 µl), y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. A la mezcla fue agregado un 60% hidruro de sodio (38 mg) bajo enfriamiento con hielo, y la mezcla fue agitada durante 30 minutos. Fue agregado a la solución de

reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con 1N ácido clorhídrico , agua,y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (380 mg). MS (m/z): 813/815 $[M+H]^+$

(3) 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (370 mg) fue disuelto en tolueno (2,5 ml), y fueron agregados a los mismos fue agregado tris(dibencilidenacetona)dipaladio (42 mg), 2-(di-terc-butilfosfino)bifenilo (27 mg), terc-butóxido de sodio (87 mg) y tetrahidrooxazina (79 µl), y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. La mezcla fue agitada a 80°C durante una hora y 45 minutos. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos el agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con un 1N de ácido clorhídrico, agua, y una solución salina saturada, fue secada sobre sulfato de

magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→1:1) para dar 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (90.3 mg, MS (m/z): 820 $[M+H]^+$) y 5-carboxipentil éster de ácido (2R,4S)-4-{[3,5-bis(triiuorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (67,7 mg, MS (m/z): 792 $[M+H]^+$).

(4) 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4dihidro-2H-quinolin-1-carboxílico (90 mg) fue disuelto en etanol (1 ml), y fueron agregados a los mismos una solución acuosa 2N de hidróxido de sodio (0,16 ml), y la mezcla fue agitada a la temperatura ambiente durante 2 horas. Fue agregado a la solución de reacción1N ácido clorhídrico (0,32 ml) y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar 5-

carboxipentil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolir-1-carboxílico (53 mg). MS (m/z): 792 $[M+H]^+$

Ejemplo 276

(1) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (1 g) fue disuelto en tolueno (3,5 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (137 mg), 2-(di-terc-butilfosfino)bifenilo (95 mg), terc-butóxido de sodio (460 mg) y tetrahidrooxazina (0,28 ml), y la mezcla fue agitada a la temperatura ambiente durante 17 horas. A la solución de reacción fueron agregados una solución acuosa saturada de carbonato hidrógeno de sodio y acetato etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (780,3 mg). MS (m/z): 634 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-

tetrahidroquinolina (300 mg) fue disuelto en diclorometano (2 ml), y fueron agregados a los mismos trietilamina (310 µl) y trifosgeno (208 mg), y la mezcla fue agitada a la temperatura ambiente durante una hora. La solución de reacción fue concentrada bajo presión reducida, y fueron agregados a los mismos dietil éter, y los materiales insolubles fueron eliminados por filtración. El filtrado fue concentrado bajo presión reducida, y el residuo resultante fue disuelto en tetrahidrofurano (2 ml), y 60% hidruro de sodio (36 mg) y terc-butil éster de ácido 3-hidroxipropiónico (131 µl) fue agregado a los mismos bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 16 horas, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→3:2) para dar 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (207 mg). MS (m/z): 806 $[M+H]^+$

(3) A 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-

2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) se agrega 4N cloruro de hidrógeno en 1,4-dioxano (2 mL), y la mezcla fue agitada durante 2 horas. La solución de reacción fue concentrada y el residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→19:1) para dar 2-carboxietil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (176,3 mg). MS (m/z):750 $[M+H]^+$

Ejemplo 277

(1) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6trifluorometil-1,2,3,4-tetrahidroquinolina (250 mg) fue disuelto en cloruro de metileno (3 ml), y fueron agregados a los mismos trietilamina (111 µl), y adicionalmente fue agregado trifosgeno (316 mg) bajo enfriamiento con hielo. Bajo atmósfera de nitrógeno, la mezcla fue agitada a la misma temperatura durante una hora, y la mezcla de reacción fue concentrada bajo presión reducida. Al residuo le fue agregado éter, y los materiales insolubles precipitados fueron eliminados por filtración. El filtrado fue concentrado bajo presión reducida, y al residuo resultante le fueron agregados tetrahidrofurano (4 ml), glicolato de metilo (62 µl) e hidruro de sodio (62,7%, 30 mg),

y la mezcla fue agitada bajo atmósfera de nitrógeno a la temperatura ambiente durante 2 horas. La mezcla de reacción fue neutralizada con una solución 10% de ácido cítrico acuosa, y a los mismos le fueron agregados una solución salina saturada, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1) para dar metoxicarbonilmetil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (166 mg). MS (m/z): 750 $[M+H]^+$

(2) metoxicarbonilmetil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[S-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (163 mg) fue disuelto en una mezcla de tetrahidrofurano (2 ml) y metanol (2 ml), y a los mismos fue agregado 1N en solución de hidróxido de sodio acuosa (1 ml), y la mezcla fue agitada a la temperatura ambiente durante una hora. La mezcla de reacción fue acidificada con una solución 10% de ácido cítrico acuosa, y fueron agregados a los mismos una solución salina saturada, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de

magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→19:1) para dar carboximetil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trilluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (125 mg). MS (m/z): 736 $[M+H]^+$

Ejemplos 278-282

Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 277 para dar los compuestos como los enumerados en la Tabla 34.

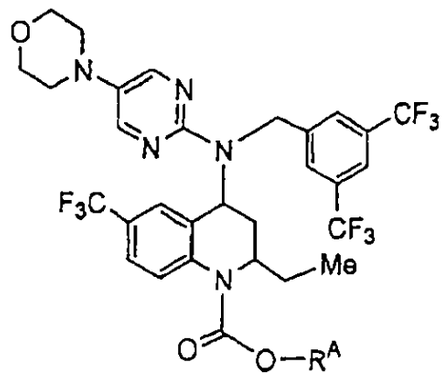
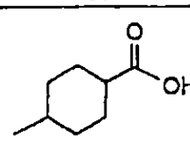
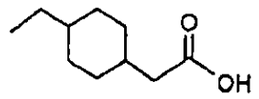
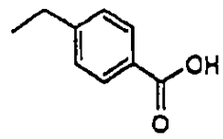


Tabla 34

Ej. No.	Configuración	R^A	Propiedades físicas, etc.
278	(2R*,4S*)		MS (m/z): 804 $[M+H]^+$
279	(2R*,4S*)		MS (m/z): 832 $[M+H]^+$
280	(2R*,4S*)		MS (m/z): 812 $[M+H]^+$

Ejemplo 283

Al [(2S,4R)-(1-terc-butoxicarbonil-2-metoxicarbonil)pirrolidin-4-il] éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinclin-1-carboxílico (230 mg), el cual es preparado tratando los compuestos de comienzo correspondientes de una manera similar al Ejemplo 277 (1), fue agregado 4N cloruro de hidrógeno en 1,4-dioxano (1,5 ml), y la mezcla fue agitada a la temperatura ambiente durante una hora y 40 minutcs. La solución de reacción fue concentrada bajo presión reducida, y el producto en bruto resultante (223 mg) fue disuelto en metanol (3 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (0,4 ml), y la mezcla fue agitada a la temperatura ambiente durante 3,5 horas. Fue agregado a la solución de reacción1N ácido clorhidrico (0,14 ml), y la mezcla fue concentrada bajo presión reducida. Al residuo resultante fue agregado dietil éter, y los materiales

insolubles fueron eliminados por filtración. El filtrado fue concentrado bajo presión reducida, y al residuo resultante fueron agregados agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue concentrada bajo presión reducida, y al residuo fueron agregados hexano y dietil éter, y la mezcla fue disuelta con calentamiento. La mezcla fue enfriada a la temperatura ambiente, y el producto polvoriento resultante fue secado bajo presión reducida para dar [(2S,4R)-2-carboxipirrolidin-4-il] éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (116 mg). MS (m/z): 791 $[M+H]^+$

Ejemplo 284

(1) (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-{5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (2,0 g) fue disuelto en tetrahidrofurano (30 ml), y fueron agregados a los mismos chroruro de acriloilo (770 µl), y trietilamina (1,4 ml) bajo enfriamiento con hielo, y la mezcla fue agitada toda la noche en la temperatura ambiente. Fue agregada a la solución de reacción una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada; fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por

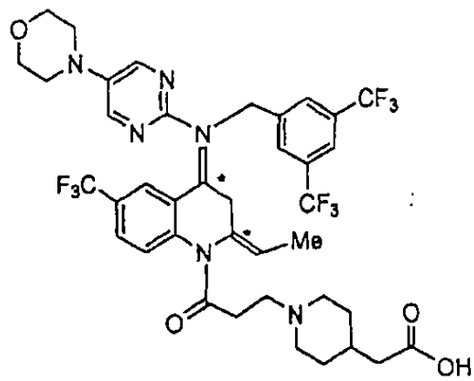
cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→3:2) para dar (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-1-acriloil-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (1,52 g). MS (m/z): 688 $[M+H]^+$

(2) (2R*,4S*)-4-({3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-1-acriloil-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (500 mg) fue disuelto en tetrahidrofurano (5 ml), y al mismo fue agregado etil éster de ácido piperidin-4-carboxílico (1,1 ml), y la mezcla fue agitada a 45°C durante 3 días. Fueron agregados a la solución de reacción una solución de cloruro de amonio acuosa saturada y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 4:1→3:2) para dar (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-[2-(4-etoxicarbonilpiperidin-1-il)etil]carbonil-6-trifluorometil-3,4-dihidro-2H-quinolina (539 mg). MS (m/z): 845 $[M+H]^+$

(3) (2R*,4S*)-4-({3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-[2-(4-

etoxicarbonilpiperidin-1-il)etil]carbonil-6-trifluorometil-3,4-dihidro-2H-quinolina (150 mg) fue disuelto en etanol (4 ml), y fueron agregados a los mismos por gotas una solución 1N de hidróxido de sodio acuosa (2 ml), y la mezcla fue agitada toda la noche a la temperatura ambiente. Fue agregado a la solución de reacción1N ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 49:1→17:3) para dar (2R*,4S*)-4-([3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-[2-(4-carboxipiperidin-1-il)etil)carbonil-6-trifluorometil-3,4-dihidro-2H-quinolina (128 mg). MS (m/z): 817 $[M+H]^+$

Ejemplo 285



Los compuestos de comienzo correspondientes fueron tratados en una manera similar al Ejemplo 284 para dar el compuesto del Ejemplo 285. MS (m/z):831 $[M+H]^+$

Ejemplo 286

(1) (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirirnidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (670 mg) fue disuelto en diclorometano (5 ml), y fueron agregados a los mismos piridina (342 µl) y metil éster de ácido 4-clorocarbonilbutírico (440 µl), y la mezcla fue agitada a la temperatura ambiente durante 24 horas. Fue agregada a la solución de reacciónagua y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar. (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-(3-metoxicarbonilpropil)carbonil-6-trifluorometil-3,4-dihidro-2H-quinolina (460,3 mg). MS (m/z): 762 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-(3-metoxicarbonilpropil)carbonil-6-trifluorometil-3,4-dihidro-2H-quinolina (100 mg) fue disuelta en una mezcla de tetrahidrofurano:metanol (1:1, 2 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (0,2

ml), y la mezcla fue agitada durante 7,5 horas. A la solución de reacción un se agrega 2N ácido clorhídrico (0,2 ml), y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar (2R*,4S*)-4-([3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-1-(3-carboxipropil)carbonil-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (92,6 mg). MS (m/z): 748 $[M+H]^+$

Ejemplo 287

(1) (2R*,4S*)-4-([3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-(3-metoxicarbonilpropil)carbonil-6-trifluorometil-3,4-dihidro-2H-quinolina (450 mg) fue disuelto en tetrahidrofurano (6 ml), y fueron agregados a los mismos 1M solución de complejo borano tetrahidrofurano en tetrahidrofurano (2,95 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 2 horas. A la solución de reacción un fue agregado dietil éter acuoso, y la mezcla fue agitada durante 30 minutos. A la mezcla se agrega acetato de etilo y agua, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en

columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin4-il)pirimidin-2-il]}amino-2-etil-1-(4-metoxicarbonilbutil)-6-trifluorometil-3,4-dihidro-2H-quinolina (90,0 mg). MS (m/z): 747 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-(4-metoxicarbonilbutil)-6-trifluorometil-3,4-dihidro-2H-quinolina (85 mg) fue disuelto en una mezcla de tetrahidrofurano:metanol (1:1, 2 ml), y fueron agregados a los mismos una solución 2N hidróxido de sodio acuosa (0,16 ml), y la mezcla fue agitada durante 4,5 horas. A la solución de reacción se agrega 2N ácido clorhídrico (0,16 ml), y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→19:1) para dar (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-1-(4-carboxibutil)-6-trifluorometil-3,4-dihidro-2H-quinolina (82 mg). MS (m/z): 732 $[M-H]^-$

Ejemplo 288

(1) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-

tetrahidroquinolina (1 g) fue disuelto en tolueno (5 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (147 mg), 2-(di-terc-butilfosfino)bifenilo (95 mg), terc-butóxido de sodio (307 mg) y una solución 2N de dimetilamina en tetrahidrofurano (1,6 ml), y la mezcla fue agitada en un recipiente sellado a la temperatura ambiente durante una hora. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar (2R,4S)4-{[3,5-bis(trifluorometil)bencil]-(5-dimetilaminopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (500 mg). MS (m/z): 592 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (470 mg) fue tratada de una manera similar a Ejemplo 276 (2)-(3) para dar 2-carboxietil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-dimetilaminopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (195.5 mg). MS (m/z): 708 $[M+H]^+$

Ejemplo 289

(1) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (7,00 g) fue disuelto en cloruro de metileno (80 ml), y fueron agregados a los mismos trietilamina (4,2 ml), y además fuen agregado trifosgeno (2,99 g) bajo enfriamiento con hielo. Bajo atmósfera de nitrógeno, la mezcla fue agitada a la misma temperatura durante 1,5 hora, y fue concentrada bajo presión reducida, y fueron agregados a los mismos éter. Los materiales insolubles precipitados fueron eliminados por filtración, y el filtrado fue concentrado bajo presión reducida. Al residuo resultante fueron agregados tetrahidrofurano (80 ml), terc-butil 3-hidroxipropionato (2,64 ml) e hidruro de sodio (62,7 %, 680 mg), y la mezcla fue agitada toda la noche a la temperatura ambiente bajo atmósfera de nitrógeno. La mezcla de reacción fue neutralizada con solución 10% de ácido cítrico acuosa, y fueron agregados a los mismos una solución salina saturada. La mezcla fue extractada con acetato de etilo, y la capa orgánica fue lavada dos veces con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 10:1) para dar 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-

etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (6,10 g). MS (m/z): 801/799 $[M+H]^+$

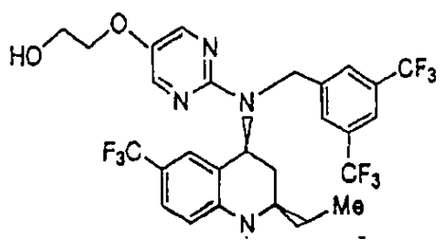
(2) 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (5,00 g) fue disuelto en dimetilsulfóxido (20 ml), y la mezcla fue desaereada. A la mezcla fueron agregados bicloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio(II) (177 mg), acetato de potasio (1,84 g) y bis(pinacolato)diboro (2,38 g), y la mezcla fue agitada a 80°C bajo atmósfera de nitrógeno durante una hora. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos una solución salina saturada y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (30 ml), y fueron agregados a los mismos por gotas una solución 30% de agua oxigenada acuosa (10 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a la misma temperatura durante una hora. A la mezcla de la reacción una solución de tiosulfato de sodio acuosa saturada fue agregada bajo enfriamiento con hielo, y la mezcla se extrae con el acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo

resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:1) para dar 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,94 g). MS (m/z): 737 $[M+H]^+$

(3) 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) fue disuelto en una mezcla de tetrahidrofurano (2.5 ml) y N,N-dimetilformamida (1 ml), y fueron agregados a los mismos 4-bromobutironitrilo (244 µl) y carbonato de potasio (281 mg), y la mezcla fue agitada a 60°C durante 1,5 hora. Fue agregada a la mezcla de la reacción una solución salina saturada, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía de gel de silicio de capa delgada (hexano:acetato de etilo = 3:1) para dar 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (107 mg). MS (m/z): 804 $[M+H]^+$

(4) 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (103 mg) fue disuelto en cloruro de metileno (1 ml), y fueron agregados a los mismos 4N ácido clorhídrico en 1,4-dioxano (1 ml) bajo enfriamiento con hielo, y la mezcla fue agitada en la temperatura ambiente durante 2 horas. La mezcla de reacción fue concentrada bajo presión reducida, y fueron agregados a los mismos una cantidad pequeña de una solución saturada de carbonato hidrógeno de sodio acuosa, y la mezcla fue neutralizada. Entonces, la mezcla fue hecha débilmente ácida con una solución acuosa 10% de ácido cítrico, y fue extractada con acetato de etilo, y la capa orgánica fue lavada dos veces con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 19:1) para dar (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico 2-carboxietil éster de ácido (71 mg). MS (m/z):748 $[M+H]^+$

Ejemplo 290



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 289 para dar el compuesto de Ejemplo 290. MS (m/z): 725 $[M+H]^+$

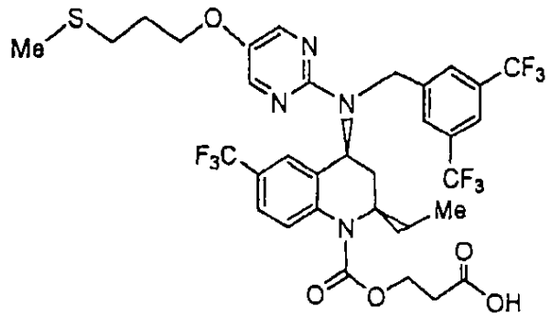
Ejemplo 291

(1) 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (220 mg) fue disuelto en tetrahidrofurano (1,5 ml), y fueron agregados a los mismos 2-metoxietanol (35 µl) y trifenilfosfina (118 mg), y a los mismos fueron agregados por gotas una solución 40% de dietil azodicarboxilato en tolueno (195 µl) bajo enfriamiento con agua. La mezcla fue agitada a la temperatura ambiente durante una hora, y a la mezcla de reacción fue agregada una solución salina saturada, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 17:3→4:1) para dar 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-

2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (193 mg). MS (m/z): 795 $[M+H]^+$

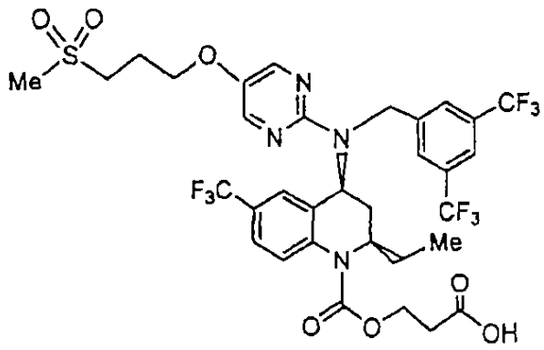
(2) A 2-terc-butoxicarboniletil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-b-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (190 mg) fueron agregados 4N ácido clorhídrico en 1,4-dioxano (2 ml), y la mezcla fue agitada en la temperatura ambiente durante 2 horas. La mezcla de reacción fue concentrada bajo presión reducida, y fueron agregados a los mismos una solución salina saturada, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada dos veces con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 19:1) para dar 2-carboxietil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-[5(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (168 mg). MS (m/z): 739 $[M+H]^+$

Ejemplo 292



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 291 para dar el compuesto de Ejemplo 292. MS (m/z): 769 $[M+H]^+$

Ejemplo 293



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 50 para dar el compuesto de Ejemplo 293. MS (m/z):801 $[M+H]^+$

Ejemplo 294

(1) 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,08 g) fue disuelto en dimetilsulfóxido (4 ml), y fueron agregados a los mismos [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio, complejo con

diclorometano (1:1, 30 mg), acetato de potasio (403 mg), y bis(pinacolato)diboro (522 mg), y la mezcla fue agitada a 80°C durante 2 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (4 ml), y fueron agregados a los mismos una solución acuosa 30% de agua oxigenada (1,0 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 7,5 horas. Fue agregada a la solución de reacción una solución de tiosulfato de sodio acuosa saturada bajo enfriamiento con hielo, y entonces además fue agregado dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,06 mg). MS (m/z): 723 $[M+H]^+$

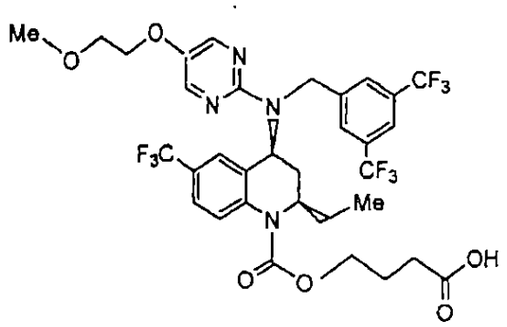
(2) 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-

etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en tetrahidrofurano (3 ml), y fueron agregados a los mismos una solución 40% de azodicarboxilato de dietilo en tolueno (255 ml), trifenilfosfina (147 mg), y 2-metoxietanol (44 µl), y la mezcla fue agitada a la temperatura ambiente durante 2 horas. Fue agregado a la solución de reacción una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→63:37) para dar 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (171,4 mg). MS (m/z): 781 $[M+H]^+$

(3) 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4dihidro-2H-quinolin-1-carboxílico (163 mg) fue disuelto en tetrahidrofurano:metanol (1:1, 4 ml), y fueron agregados a los mismos una solución 2N de hidróxido de sodio acuosa (0,315 ml), y la mezcla fue agitada a la temperatura ambiente durante 15,5 horas. A la

solución de reacción fue agregado 1N ácido clorhídrico (0,63 ml), y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→24:1) y además por columna de cromatografía en infiltración de gel (JAIGEL-1H, y JAIGEL-2H, fabricado "Japan Analitic Industry Co., Ltd."; 4 ml/min., cloroformo) para dar 4-carboxibutil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (36.5 mg). MS (m/z): 767[M+H]$^+$

Ejemplo 295



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 294 para dar el compuesto de Ejemplo 295: MS (m/z): 753 [M+H]$^+$

Ejemplo 296

(1) 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico

(400 mg) fue disuelto en dimetilsulfóxido (1,5 ml), y fueron agregados a los mismos [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio, complejo con diclorometano (1:1, 11 mg), acetato de potasio (145 mg), y bis(pinacolato)diboro (187 mg), y la mezcla fue agitada a 80°C durante 2 horas y 20 minutos. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (1,5 ml), y fueron agregados a los mismos una solución 30% de agua oxigenada acuosa (0,56 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a temperatura ambiente durante 1,5 hora. A la mezcla de reacción fue agregada una solución de tiosulfato de sodio acuosa saturada bajo enfriamiento con hielo, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→7:3) para dar 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirirnidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico

(319 mg). MS (m/z): 751 $[M+H]^+$

(2) 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirirnidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (310 mg) fue disuelto en N,N-dimetilformamida (4 ml), y fueron agregados a los mismos carbonato de potasio (340 mg) y 2-bromoetanol (160 ul) y la mezcla fue agitada a la temperatura ambiente durante 23,5 horas. Fue agreçado a la solución de reacción una solución de ácido cítrico acuosa saturada y acetato de etilo, hexano, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (146 mg). MS (m/z): 795 $[M+H]^+$

(3) 5-etoxicarbonilpentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (130 mg) fue disuelto en etanol (1,6 ml), y fueron agregados a los mismos una solución de 2N hidróxido de sodio acuosa (0,25 ml), y la mezcla fue agitada a la

temperatura ambiente durante 4 horas. A la solución de reacción fue agregada 2N ácido clorhídrico, y la capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo: metanol = 1:0→19:1) para dar 5-carboxilpentil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (119 mg). MS (m/z): 767 $[M+H]^+$

Ejemplo de referencia 1

A una solución de azida de sodio (19,2 g) en agua (75 ml) fue agregado por gotas bajo enfriamiento con hielo una solución de cloruro de acriloilo (20 ml) en tolueno (75 ml), y la mezcla fue agitada a la misma temperatura durante 3 horas. Una solución acuosa saturada de carbonato hidrógeno de sodio fue agregada a los mismos, y la capa orgánica fue lavada con una solución salina saturada y fue secada sobre sulfato de magnesio. La solución de tolueno resultante fue agregada por gotas en una mezcla de (S)-1-feniletil alcohol (38,6 ml), piridina (9,9 ml) y hidroquinona (1,49 g) lo cual fue calentado a 85°C, y la mezcla fue agitada a la misma temperatura durante 2 horas. A la mezcla se permite enfriar a la temperatura ambiente, y fueron agregados a los mismos una

solución acuosa saturada de carbonato hidrógeno de sodio. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 8:1) para dar (S)-1-feniletil éster de ácido vinilcarbámico (28,9 g). MS (m/z): 191 $[M]^+$

Ejemplo de referencia 2

(1) A una solución de p-anisidina (50 g) y benzotriazol (48,4 g) en tolueno (700 ml) fueron agregados por gotas una solución de propionaldehído (32,2 ml) en tolueno (40 ml) bajo enfriamiento con hielo, y la mezcla fue agitada toda la noche a la temperatura ambiente. A la mezcla heptano fue agregado (700 ml), y la mezcla fue agitada adicionalmente durante una hora. El precipitado fue recolectado por filtración, fue lavado con heptano para dar {[(1-benzotriazol-1-il)propil]-(4-metoxifenil)}amina (105,8 g).

(2) {[1-(Benzotriazol-1-il)propil]-(4-metoxifenil)}amina (45,8 g), (S)-1-feniletil éster de ácido vinilcarbámico (31 g) y ácido p-toluensulfónico (616 mg) fue disuelto en el tolueno (500 ml), y la mezcla fue agitada a 80°C durante 4 horas. A la mezcla se agregan una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo

presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 6:1→3:1) para dar una mezcla (46,4 g) de (2R,4S)-(2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-1,2,3,4-tetrahidroquinolina y (2S,4R)-2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-1,2,3,4-tetrahidroquinolina. MS (m/z): 355 $[M+H]^+$.

(3) Una mezcla (45,1 g) de (2R,4S)-2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-1,2,3,4-tetrahidroquinolina y (2S,4R)-2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-1,2,3,4-tetrahidroquinolina fue recristalizada de isopropil éter (150 ml) para dar (2R,4S)-(2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-1,2,3,4-tetrahidroquinolina (9,56 g). MS (m/z): 355 $[M+H]^+$.

(4) (2R,4S)-(2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-1,2,3,4-tetrahidroquinolina (7,5 g) y piridina (8,56 ml) fueron disueltos en cloruro de metileno (75 ml), y fueron agregados a los mismos por gotas una solución de clorocarbonato de etilo (10,1 ml) en cloruro de metileno (20 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a temperatura ambiente durante 3 horas. La solución de reacción fue lavada con una solución 1M de hidróxido de sodio acuosa, 1N ácido clorhídrico, y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue

purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 90:10→60:40) para dar etil éster de ácido (2R,4S)-2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-3,4-dihidro-2H-quinolin-1-carboxílico (7,61 g). MS (m/z): 444 $[M+NH_4]^+$.

(5) a una solución de etil éster de ácido (2R,4S)-2-etil-6-metoxi-4-((S)-1-feniletoxicarbonilamino)-3,4-dihidro-2H-quinolin-1-carboxílico (9,32 g) en etanol (100 ml) fue agregado 10% paladio carbono, y la mezcla fue agitada bajo atmósfera de hidrógeno durante 3 horas. El catalizador fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida para dar etil éster de ácido (2R,4S)-4-amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (6,09 g). MS (m/z): 279 $[M+H]^+$.

Ejemplo de referencia 3

(1) 3,4-Etilendioxianilina (17,68 g) y benzotriazol (13,93 g) fue disuelto en tolueno (200 ml), y fueron agregados a los mismos propionaldehído por gotas (9,2 ml) bajo enfriamiento con hielo. La solución de reacción fue agitada toda la noche a la temperatura ambiente. A la mezcla fue agregado heptano (200 ml), y la mezcla fue agitada además durante una hora. El precipitado fue recolectado por filtración, y fue lavado con heptano para dar {[1-(benzotriazol-1-il)propil]-(3,4-etilendioxifenil)}amina (35,48 g).

(2) ([1-(Benzotriazol-1-il)propil]-(3,4-etilendioxifenil)} el

amina (30,00 g), bencil éster de ácido vinilcarbámico (17,13 g), y ácido p-toluensulfónico (184 mg) fueron disueltos en tolueno (310 ml), y la mezcla fue agitada a 70°C durante 3 horas. A la mezcla fueron agregados una solución 1N hidróxido de sodio acuosa y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (cloroformo:acetona = 20:1) para dar (2R*,4S*)-4-benciloxicarbonilamino-2-etil-6,7-etilendioxi-1,2,3,4-tetrahidroquinolina (5,63 g). MS (m/z): 369 $[M+H]^+$.

(3) ((2R*,4S*)-4-benciloxicarbonilamino-2-etil-6,7-etilendioxi-1,2,3,4-tetrahidroquinolina (5,62 g) y piridina (6,2 ml) fueron disueltos en cloruro de metileno (45 ml), y fueron agregados a los mismos por gotas una solución de clorocarbonato de etilo (7,3 ml) en cloruro de metileno (15 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 3 horas. Fue agregada a la solución de reacción una solución 1N de hidróxido de sodio acuosa (83 ml), y la mezcla fue agitada a la temperatura ambiente durante 30 minutos. La mezcla fue separada y la capa orgánica fue lavada con un 1N ácido clorhídrico, una solución acuosa saturada de carbonato hidrógeno de sodio, y una solución salina saturada, fue secada sobre sulfato de sodio,

y fue concentrada bajo presión reducida. El residuo fue disuelto en etanol (40 ml), y fueron agregados a los mismos por gotas agua (17 ml). Los cristales precipitados fueron recolectados por filtración, y fueron lavados con una mezcla de etanol-agua = 7:3 para dar etil éster de ácido (2R*,4S*)-2-etil-6,7-etilendioxi-4-benciloxicarbonilamino-3,4-dihidro-2H-quinolin-1-carboxílico (5.98 g). MS (m/z): 458 $[M+H_2O]^+$.

(4) Etil éster de ácido (2R*,4S*)-4-benciloxicarbonilamino-2-etilendioxi-4-3,4-dihidro-2H-quinolin-1-carboxílico (5,97 g) fue disuelto en metanol (60 ml), y fueron agregados a los mismos 10% paladio carbono (0,5 g) y formiato de amonio (2,14 g), y la mezcla fue agitada a 37°C por una hora. El paladio carbono fue eliminado por filtración, y el filtrado fue concentrado bajo presión reducida. El residuo fue disuelto en cloroformo (65 ml), y lavado con una solución acuosa saturada de carbonato hidrógeno de sodio y una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. Al residuo resultante fue agregado heptano (20 ml), y la mezcla fue agitada toda la noche. Los cristales precipitados fueron recolectados por filtración y fueron lavados con heptano para dar etil éster de ácido (2R*,4S*)-4-amino-2-etil-6,7-etilendioxi-3,4-dihidro-2H-quinolin-1-carboxílico (3,54 g). MS (m/z): 307 $[M+H]^+$.

Ejemplo de referencia 4

A etil éster de ácido (2R*,4S*)-6-bromo-2-etil-4-(benciloxicarbonilamino)-3,4-dihidro-2H-quinolin-1-carboxílico (28,36 g) que fue preparado tratando los compuestos de comienzo correspondientes de una manera similar al Ejemplo de referencia 3 (1)-(3), fueron agregados una solución 25% de bromuro hidrógeno en ácido acético (140 ml), y la mezcla fue agitada a la temperatura ambiente durante 45 minutos. La solución de reacción fue concentrada bajo presión reducida, y fue agregado al residuo éter (200 ml), y el precipitado fue recolectado por filtración y lavado con éter. El precipitado fue agregado a una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (acetato de etilo) y fue concentrada. Al residuo fue agregado heptano (150 ml), y la mezcla fue agitada toda la noche a la temperatura ambiente. El precipitado fue recolectado por filtración y lavado con heptano para dar etil éster de ácido (2R*,4S*)-4-amino-6-bromo-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (18,46 g). MS (m/z): 327/329 $[M+H]^+$.

Ejemplo de referencia 5

(1) El bromopiruvato de etilo (29,9 g) y urea (13,8 g) fueron disueltos en etanol (110 ml) y la mezcla permaneció a reflujo

durante 24 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fue concentrada bajo presión reducida. Al residuo fueron agregados agua y éter, y el valor de pH de la mezcla fue ajustado a 10 por agregado de una solución 2N de hidróxido de sodio acuosa. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue cristalizado del isopropil éter para dar etil éster de ácido 2-aminooxazol-4-carboxílico (7,53 g). MS (m/z): 157[M+H]$^+$.

(2) etil éster de ácido 2-Aminooxazol-4-carboxílico (7,3 g), nitrito de terc-butilo (9,4 ml), y cloruro de cobre (II) (9,4 g) fue disuelto en acetonitrilo (210 ml), y la mezcla fue agitada a 60-80°C durante 2 horas. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos una solución 2N de ácido clorhídrico acuosa y cloruro de metileno. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→2:1) para dar etil éster de ácido 2-clorooxazol-4-carboxílico (5,57 g). MS (m/z): 176/178 [M+H]$^+$.

Ejemplo de referencia 6

El etil éster de ácido 2-amino-4-metiltiazol-5-carboxílico (8,72 g), nitrito de terc-butilo (9,4 ml) y

cloruro de cobre (II) (9,4 g) fue disuelto en acetonitrilo (210 ml), y la mezcla fue agitada a 80°C durante 2 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos una solución 2N de ácido clorhídrico acuosa y cloruro de metileno, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 99:1→23:2) para dar etil éster de ácido 2-cloro-4-metiltiazol-5-carboxílico (8,83 g). MS (m/z): 206/208 $[M+H]^+$.

Ejemplo de referencia 7

(1) Etil éster de ácido 4-oxociclohexancarboxílico (5 g) fue disuelto en etanol (20 ml), y fueron agregados a los mismos hidróxido de sodio (1,29 g), y la mezcla fue agitada a la temperatura ambiente durante una hora. Fue agregado a la mezcla dietilfosfonoacetato de etilo (6,4 ml), y fueron agregados a los mismos por gotas adicionalmente una solución 21% de etóxido de sodio en etanol (12 ml) bajo enfriamiento con hielo durante un período de 30 minutos. La solucion de reacción fue agitada bajo enfriamiento con hielo durante 3,5 horas, y fue concentrada bajo presión reducida. Al residuo resultante fueron agregados 2N ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada

con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→1:1) para dar ácido 4-(etoxicarbonilmetilen)ciclohexancarboxílico (2,05 g) como un producto en bruto. MS (m/z): 213 $[M+H]^+$.

(2) El ácido 4-(etoxicarbonilmetilen)ciclohexancarboxílico en bruto (2,05 g) fue disuelto en etanol (20 ml), y fueron agregados a los mismos 10% paladio-carbono (500 mg), formiato de amonio (3,7 g) y ácido acético (4,2 ml), y la mezcla fue agitada toda la noche a 60°C. La solución de reacción fue enfriada a la temperatura ambiente, y la solución de reacción fue filtrada. Al filtrado se agregan 2N ácido clorhídrico y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 7:3→1:1) para dar ácido 4-(etoxicarbonilmetil)ciclohexancarboxílico (1,97 g). MS (m/z): 215 $[M+H]^+$.

(3) El ácido 4-(Etoxicarbonilmetil)ciclohexancarboxílico (1,97 g) fue disuelto en tetrahidrofurano (20 ml), y fueron agregados a los mismos clorocarbonato de etilo (650 µl) y trietilamina (950 µl) bajo enfriamiento con hielo, y la

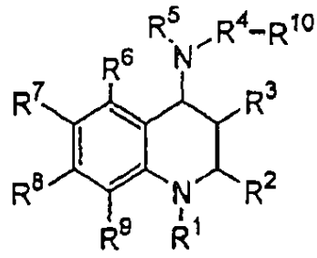
mezcla fue agitada bajo enfriamiento con hielo durante 30 minutos. La solución de reacción fue filtrada, y el filtrado fue agregado a una suspensión de borohidruro de sodio (515 mg) en tetrahidrofurano (10 ml), y la mezcla fue agitada bajo enfriamiento con hielo durante una hora. Se agregan 1N ácido clorhídrico y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar acetato de etil 4-(hidroximetil)ciclohexano (360 mg). MS (m/z): 201 $[M+F]^+$.

Ejemplo de referencia 8

Los compuestos de comienzo correspondientes fueron tratados de una manera similar al Ejemplo de referencia 3 para dar etil éster de ácido (2R*,4S*)-4-amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico.

REIVINDICACIONES

1. Un compuesto caracterizado por que posee la fórmula (1):



(I)

en donde R^1 es un átomo de hidrógeno, un grupo alcoxicarbonilo opcionalmente sustituido, un grupo carbamoilo opcionalmente sustituido, un grupo alquilo opcionalmente sustituido, un grupo alcanoilo opcionalmente sustituido, un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de oxigeno, azufre y átomos de nitrógeno (el grupo heterocíclico es opcionalmente sustituido), o un grupo carbonilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo heterocíclico opcionalmente sustituido),;

R^2 es un átomo de hidrógeno o un grupo alquilo opcionalmente sustituido;

R^3 es un átomo de hidrógeno o un grupo alquilo opcionalmente sustituido;

R^4 es un grupo alquileno opcionalmente sustituido;

R^5 es un grupo monocíclico o heterocíclico bicíclico

saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno, en donde el grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes, o dicho grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de grupos siguientes y además por un átomo halógeno, un grupo oxo y/o hidroxilo:

grupo ciano, grupo nitro, grupo carboxilo, grupo sulfo, grupo alquilo C_{3-10}, grupo alquilo sustituido, grupo cicloalquilo opcionalmente sustituido, grupo alquenilo opcionalmente sustituido, grupo alcoxilo C_{3-10}, grupo alcoxilo sustituido, grupo cicloalcoxilo opcionalmente sustituido, grupo alcoxicarbonilo opcionalmente sustituido, grupo carbamoilo opcionalmente sustituido, grupo carbamimidoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, grupo alquilsulfinilo opcionalmente sustituido, grupo alquilsulfonilo opcionalmente sustituido, grupo amino opcionalmente sustituido, grupo sulfamoilo opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno (el grupo heterocíclico es opcionalmente sustituido), un grupo oxilo monocíclico o

heterocíclico bicíclico saturados o no saturado que contiene 1 a 4 heteroátomos seleccionados independientemente de átomos de oxígeno, azufre y nitrógeno (el grupo oxilo heterocíclico es opcionalmente sustituido), y un grupo carbonilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo carbonilo heterocíclico es opcionalmente sustituido);

R^6, R^7, R^8 y R^9 son independientemente un átomo de hidrógeno, un átomo halógeno, un grupo hidroxilo, un grupo nitro, un grupo ciano, un grupo alquilo opcionalmente sustituido, un grupo alcoxilo opcionalmente sustituido, un grupo alquilsulfoniloxilo opcionalmente sustituido o un grupo amino opcionalmente sustituido; o

R^6 y R^7, ó R^7 y R^8, ó R^8 y R^9 pueden combinarse en los extremos para formar un grupo alquileno cuyo grupo alquileno puede contener 1 a 3 heteroátomos independientemente seleccionados de los átomos de nitrógeno, azufre y oxígeno, y puede tener un sustituyente(s); y

R^{10} es un anillo aromático que contiene opcionalmente 1 a 3 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el anillo aromático es opcionalmente sustituido), o una sal farmacéuticamente

aceptable del mismo.

2. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que R^5 es un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno, en donde el grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes, o dicho grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes junto con átomo halógeno, grupo oxo y/o hidroxilo:

grupo ciano, grupo nitro, grupo carboxilo, grupo sulfo, grupo alquilo C_{3-10}, grupo alquilo sustituido, grupo cicloalquilo opcionalmente sustituido, grupo alquenilo opcionalmente sustituido, grupo alcoxilo C_{3-10}, grupo alcoxilo sustituido, grupo cicloalcoxilo opcionalmente sustituido, grupo alcoxicarbonilo opcionalmente sustituido, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido, grupo carbamidoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, grupo alquilsulfinilo opcionalmente sustituido, grupo alquilsulfonilo opcionalmente sustituido, grupo amino, grupo mono- o dialquilamino opcionalmente sustituido, grupo alcanoilamino opcionalmente sustituido, grupo

alcoxicarbonilamino opcionalmente sustituido, grupo alquilsulfonilamino opcionalmente sustituido, grupo mono- o di-alquilcarbamoilamino opcionalmente sustituido, un grupo carbonilamino monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo carbonilamino heterocíclico es opcionalmente sustituido), grupo sulfamoilo, grupo mono o di-alquil sulfamoilo opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo heterocíclico opcionalmente sustituido), un grupo oxilo monocíclico o heterocíclico bicíclico saturados o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo oxilo heterocíclico es opcionalmente sustituido), y un grupo carbonilo monocíclico o bicíclico heterocíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo carbonilo heterocíclico es opcionalmente sustituido); y

R^{10} es un anillo aromático que opcionalmente contiene 1 a 3 heteroátomos independientemente seleccionado de átomos de oxígeno, azufre y nitrógeno, cuyo anillo aromático es opcionalmente sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes: átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo opcionalmente sustituido, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido, grupo alquilo opcionalmente sustituido, grupo alcoxilo opcionalmente sustituido, grupo hidroxilo, grupo nitro, grupo ciano, grupo amino, grupo mono- o dialquilamino opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, y un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroatomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo heterocíclico opcionalmente sustituido).

3. Un compuesto de acuerdo con la reivindicación 2, caracterizado por que sustituyente(s) para el grupo alquilo sustituido, grupo alquilo opcionalmente sustituido, grupo cicloalquilo opcionalmente sustituido, grupo alquenilo opcionalmente sustituido, grupo alcoxilo sustituido, grupo alcoxilo opcionalmente sustituido, grupo cicloalcoxilo opcionalmente sustituido, grupo alcoxicarbonilo opcionalmente sustituido, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, grupo

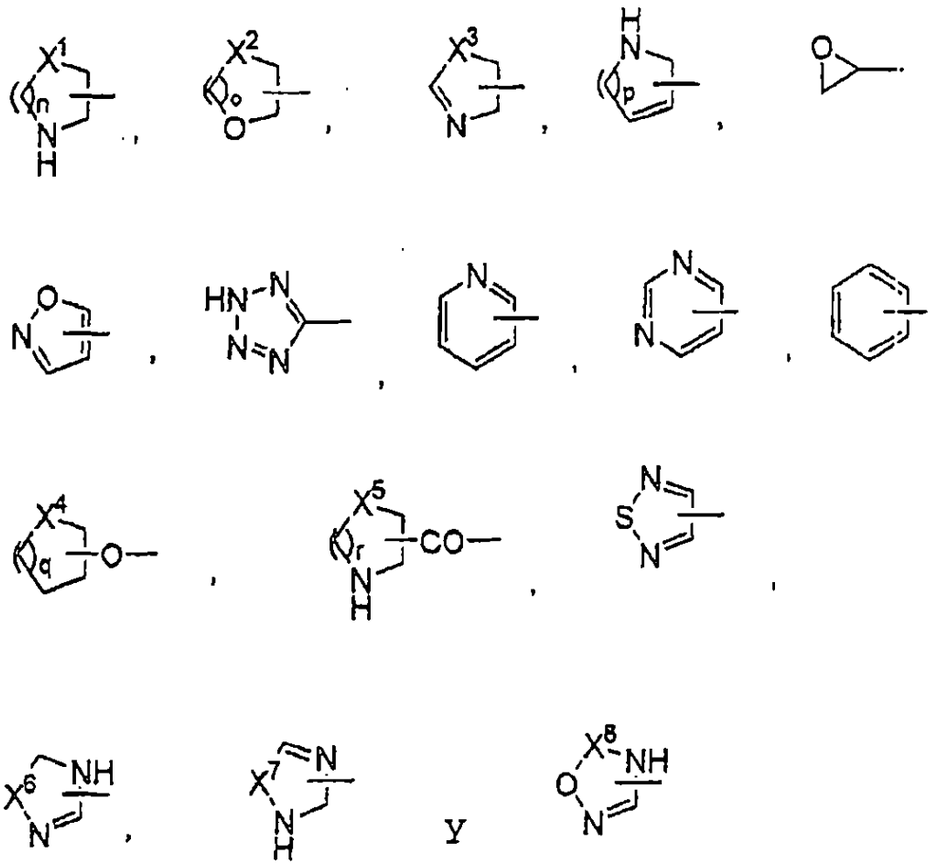
alquilsulfinilo opcionalmente sustituido, grupo alquilsulfonilo opcionalmente sustituido, grupo mono- o di-alquilamino opcionalmente sustituido; grupo alcanoilamino opcionalmente sustituido, grupo alcoxicarbonilamino opcionalmente sustituido, grupo alquilsulfonilamino opcionalmente sustituido, grupo mono- o di-alquilcarbamoilamino opcionalmente sustituido, grupo mono- o di-alquilsulfamoilo opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, grupo alquileno opcionalmente sustituido, un grupo carbonilamino monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo carbonilamino heterocíclico es opcionalmente sustituido), un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo heterocíclico opcionalmente sustituido), un grupo oxilo monocíclico o heterocíclico de bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno (el grupo oxilo heterocíclico es opcionalmente sustituido), y un grupo carbonilo monocíclico o bicíclico heterocíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre

y nitrógeno (el grupo de carbonilo heterocíclico es opcionalmente sustituido) puede ser 1-5 grupos seleccionados de los grupos siguientes:

átomo halógeno; grupo ciano; grupo hidroxilo; grupo nitro; grupo carboxilo; grupo oxo; grupo tioxo; grupo sulfo; grupo cicloalquilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o dialquilamino, grupo fenilo o morfolinilo; grupo alcoxicarbonilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o morfolinilo; grupo carbamoilo; grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o morfolinilo; grupo alquilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o morfolinilo; grupo alcanoilo opcionalmente sustituido por hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alcoxilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo,

grupo mono- o di-alquilamino, grupo fenilo o morfolinilo; grupo alcanoiloxilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alquiltio opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alquilsulfonilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo alquilsulfinilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo mono- o di-alquilsulfamoilo opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo amino; grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo mono- o di-alquilsulfamoilamino opcionalmente sustituido por grupo

hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono- o di-alquilamino, grupo fenilo o grupo morfolinilo; grupo mono- o di-alquilureido opcionalmente sustituido por grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo mono o di-alquilamino, grupo fenilo o grupo morfolinilo; y un grupo de la fórmulas:



en donde X^1 y X^3 son independientemente CH_2, NH, O, S, SO o SO_2; X^2 y X^5 son independientemente CH_2, O, S, SO o SO_2; X^4 es NH, O, S, SO o SO_2; X^6 y X^7 son independientemente O ó S; X^8 es S ó SO; y n, o, p, q y r son

independientemente un entero de valor 1 a 4, en donde cada de grupo de la fórmula anterior es opcionalmente sustituido por 1 a 3 sustituyentes seleccionados de los grupos siguientes:

átomo halógeno, grupo carboxilo, grupo hidroxilo. grupo ciano, grupo oxo, los tioxo grupo, grupo alquilo, grupo hidroxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialquilo, grupo morfolinilalquilo, grupo fenilalquilo, grupo alcanoilo, grupo hidroxialcanoilo, grupo alcoxialcanoilo, grupo alcoxilo, grupo fenilalcoxilo, grupo alcoxicarbonilo, grupo benciloxicarbonilo, grupo mono- o di-alquilamino, grupo mono- o di-alquilcarbamoilo, grupo mono- o di-alquilsulfamoilo, grupo alquilsulfonilo y grupo tetrazolilo.

4. Un compuesto de acuerdo con la reivindicación 3, caracterizado por que el "anillo aromático que opcionalmente contiene 1 a 3 heteroátomos seleccionado independientemente de átomos de oxígeno, azufre y nitrógeno" es un grupo fenilo, naftilo, piridilo, quinolilo, isoquinolilo, furilo, pirimidinilo, triazolilo o tienilo;

el "grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 hetercátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno" es un grupo morfolinilo, tiomorfolinilo, piperazinilo, pirrolidinilo, piperidinilo, hexahidroazepinilo,

pirrolinilo, imidazolidinilo, oxazolidinilo, tetrahidropiranilo, tetrahidrofuranilo, dioxolanilo, oxiranilo, pirimidinilo, piridilo, triazolilo, tetrazolilo, oxadiazolilo, dihidropirimidinilo, pirazinilo, tiazolilo, oxazolinilo, oxazolilo, piridazinilo, imidazolinilo, imidazolilo, pirazinilo, tienilo, pirrolilo, furilo o dihidrooxazinilo;

el "grupo oxilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno" es un grupo morfoliniloxilo, piperaziniloxilo, tiomorfoliniloxilo, pirrolidiniloxilo, piperidiniloxilo, hexahidroazepiniloxilo, pirroliniloxilo, imidazolidiniloxilo, oxazolidiniloxilo, tetrahidropiraniloxilo, tetrahidrofuraniloxilo, dioxolaniloxilo, oxiraniloxilo, pirimidiniloxilo, piridiloxilo, triazoliloxilo, tetrazoliloxilo, oxadiazoliloxilo, dihidropirimidiniloxilo, piraziniloxilo, tiazoliloxilo, oxazoliniloxilo, oxazoliloxilo, piridaziniloxilo, imidazoliniloxilo, imidazoliloxilo, piraziniloxilo, tieniloxilo, pirroliloxilo, furiloxilo o dihidrooxaziniloxilo;

el "grupo carbonilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno" es un grupo morfolinilcarbonilo,

piperazinilcarbonilo, tiomorfolinilcarbonilo, pirrolidinilcarbonilo, piperidinilcarbonilo, hexahidroazepinilcarbonilo, pirrolinilcarbonilo, imidazolidinilcarbonilo, oxazolidinilcarbonilo, tetrahidropiranilcarbonilo, tetrahidrofuranilcarbonilo, dioxolanilcarbonilo, pirimidinilcarbonilo, oxiranilcarbonilo, piridilcarbonilo, triazolilcarbonilo, tetrazolilcarbonilo, oxadiazolilcarbonilo, dihidropirimidinilcarbonilo, pirazinilcarbonilo, tiazolilcarbonilo, oxazolinilcarbonilo, oxazolilcarbonilo, piridazinilcarbonilo, imidazolinilcarbonilo, imidazolilcarbonilo, pirazinilcarbonilo, tienilcarbonilo, pirrolilcarbonilo., furilcarbonilo o dihidrooxazinilcarbonilo; y

el "grupo carbonilamino monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionado de átomos de oxígeno, azufre y nitrógeno" es un grupo morfolinilcarbonilamino, tiomorfolinilcarbonilamino, piperazinilcarbonilamino, pirrolidinilcarbonilamino, piperidinilcarbonilamino, hexahidroazepinilcarbonilamino, pirrolinilcarbonilamino, imidazolidinilcarbonilamino, oxazolidinilcarbonilamino, tetrahidropiranilcarbonilamino, tetrahidrofuranilcarbonilamino, dioxolanilcarbonilamino, oxiranilo, carbonilamino, pirimidinilcarbonilamino, piridilcarbonilamino, triazolilcarbonilamino,

tetrazolilcarbonilamino, oxadiazolilcarbonilamino, dihidropirimidinilcarbonilamino, pirazinilcarbonilamino, tiazolilcarbonilamino, oxazolinilcarbonilamino, oxazolilcarbonilamino, piridazinilcarbonilamino, imidazolinilcarbonilamino, imidazolilcarbonilamino, pirazinilcarbonilamino, tienilcarbonilamino, pirrolilcarbonilamino, furilcarbonilamino o dihidrooxazinilcarbonilamino.

5. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que R^1 es un átomo de hidrógeno; un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo alquiltio, grupo alquilsulfonilo, grupo alquenilo, grupo amino, grupo mono- o di-alquilamino, grupo tetrazolilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo (dicho grupo mono- o di-alquilcarbamoilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo y grupo alcoxicarbonilo), grupo alcanoilamino

(dicho grupo alcanoilamino es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo hidroxilo y átomo halógeno), átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o dialquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o dialquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo morfolinilo opcionalmente sustituido por grupo oxo, grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y los grupo alcoxicarbonilalcoxilo), grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3

sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o dialquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), y grupo pirimidinilo (dicho grupo pirimidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo); un grupo carbamoilo opcionalmente sustituido por grupo alcoxilo; un grupo dihidrooxazolilo opcionalmente sustituido por 1 a 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; un grupo dihidroimidazolilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; un grupo dihidrooxazinilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por 1 a 5

sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- o di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo); un grupo alquilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- ó di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo del fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo); un grupo alcanoilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente

seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- o di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo); un grupo morfolinilcarbonilo; un grupo piperazinilcarbonilo opcionalmente sustituido por grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilalquilo;

un grupo pirrolidinilcarbonilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo; o un grupo piperidinilcarbonilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo;

R^5 es un grupo heterocíclico saturado o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre

y nitrógeno;

en donde dicho grupo heterocíclico es sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes, o dicho grupo heterocíclico es sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes junto con un átomo halógeno, un grupo oxo y/o hidroxilo:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo cicloalquilo opcionalmente sustituido por grupo carboxilo o alcoxicarbonilo;

grupo alquilo C_{3-10};

grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo mono- o di-alquilcarbamoilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo fenilo, carboxilo o hidroxilo), grupo alcanoilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino opcionalmente sustituido por grupo carboxilo o alcoxilo, grupo mono- o di-alquilsulfamoilamino, grupo mono- o dialquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo dioxolanilo opcionalmente sustituido por

grupo alquilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo morfolinilo, y grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo;

grupo alquenilo opcionalmente sustituido por un grupo seleccionado del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo benciloxicarbonilo, y grupo tetrazolilo;

grupo alqueniloxilo opcionalmente sustituido por grupo carboxilo;

grupo alcoxilo C_{3-10};

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo carbamoilo, grupo *mono-* o di-alquilcarbamoilo (dicho grupo *mono-* o di-alquilcarbamoilo es opcionalmente sustituido por carboxilo, grupo alcoxicarbonilo o hidroxilo), grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo carboxilo, formilo o hidroxilo), grupo alcanoiloxilo. grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo,

grupo aminosulfonilo, grupo amino, grupo mono- o di-alquilamino sustituido por grupo carboxilo o alcoxilo, grupo mono- o di-alquilsulfamoilamino, grupo mono- o dialquilureido opcionalmente sustituido por grupo morfolinilo, grupo cicloalquilo opcionalmente sustituido por grupo carboximetilo, grupo oxiranilo, grupo fenilo opcionalmente sustituido por grupo alcoxilo o carboxilo, grupo morfolinilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo pirrolidinilo sustituido por grupo oxo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo pirimidinilo, grupo piridilo, grupo dioxolanilo opcionalmente sustituido por grupo alquilo, grupo oxadiazolilo opcionalmente sustituido por grupo oxo, grupo oxatiadiazolilo opcionalmente sustituido por grupo oxo, grupo pirrolidinilcarbonilo opcionalmente sustituido por grupo carboxilo, grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo, y grupo morfolinilcarbonilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo fenilo; grupo carbamoilo;

grupo mono- o di-alquilcarbamoilo opcionalmente

sustituido por un grupo seleccionado del grupo carboxilo, grupo morfolinilo y grupo alcoxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio opcionalmente sustituido por un grupo seleccionado del grupo hidroxilo, grupo carboxilo y grupo mono- o di-alquilcarbamoilo;

grupo alquilsulfinilo;

grupo alquilsulfonilo opcionalmente sustituido por un grupo seleccionado del grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo y grupo mono- o di-alquilcarbamoilo;

grupo amino;

grupo mono- o di-alquilamino opcionalmente sustituido por un grupo seleccionado del grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino y grupo morfolinilo;

grupo mono- o di-alcanoilamino opcionalmente sustituido por un grupo seleccionado del grupo hidroxilo, grupo alcoxilo, grupo carboxilo y grupo amino;

grupo mono- o di-alquilcarbamoilamino opcionalmente sustituido por grupo alcoxilo;

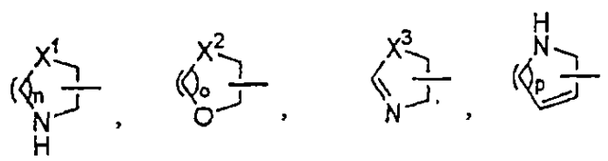
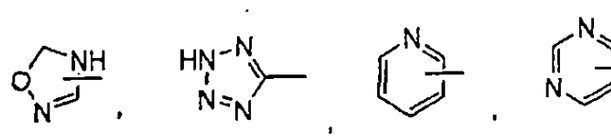
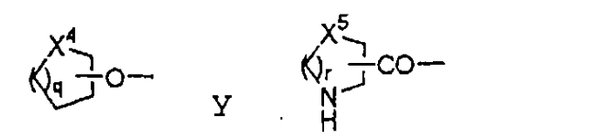
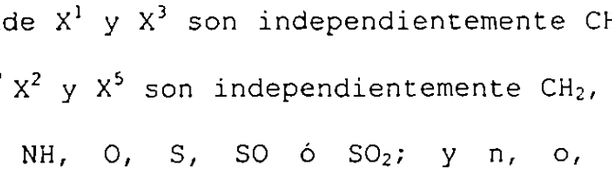
grupo morfolinilcarbonilamino;

grupo sulfamoilo;

grupo mono- o di-alquilsulfamoilo;

grupo alcanoilo opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo, grupo

alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alqui..amino y los grupo morfolinilo; o un grupo seleccionado de los grupos siguientes:

en donde X^1 y X^3 son independientemente CH_2, NH, O, S, SO ó SO_2; X^2 y X^5 son independientemente CH_2, O, S, SO ó SO_2; X^4 es NH, O, S, SO ó SO_2; y n, o, p, q y r son independientemente un entero de valor 1 a 4, en donde cada grupo de la fórmula anterior es opcionalmente sustituido por un sustituyente(s) seleccionado de los grupos siguientes:

grupo carboxilo, grupo hidroxilo, grupo ciano, grupo oxo, grupo alquilo, grupo hidroxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialquilo, grupo morfolinilalquilo, grupo fenilalquilo, grupo alcanoilo, grupo hidroxialcanoilo, grupo alcoxialcanoilo, grupo alcoxilo, grupo fenilalcoxilo, grupo alcoxicarbonilo,

grupo benciloxicarbonilo, grupo mono- o di-alquilamino, grupo mono- o di-alquilcarbamoilo, grupo mono- o di-alquilsulfamoilo, grupo alquilsulfonilo y grupo tetrazolilo;

R^6, R^7, R^8 y R^9 son independientemente un átomo de hidrógeno, un átomo halógeno, un grupo hidroxilo, un grupo nitro, un grupo ciano, un grupo alquilo, un grupo alcoxilo, o un grupo mono- o di-alquilamino, en donde dichos grupos alquilo, alcoxilo y mono- o di-alquilamino son opcionalmente sustituidos por 1 a 6 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo alcoxilo, grupo alquiltio, grupo amino, grupo nitro, grupo ciano, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo y grupo mono- o di-alquilamino; o

R^6 y R^7, ó R^7 y R^8, ó R^8 y R^9 pueden combinarse en los extremos para formar un grupo alquileno y dicho grupo alquileno puede contener 1 a 3 heteroátomos independientemente seleccionados de los átomos de nitrógeno, azufre y oxígeno;

R^{10} es un anillo monocíclico aromático que opcionalmente contiene 1 a 3 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno;

en donde el anillo monocíclico aromático es opcionalmente sustituido por 1 a 4 sustituyentes independientemente seleccionados del átomo halógeno, grupo carboxilo, grupo

alcoxicarbonilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo, grupo alquilo, grupo alcoxilo, grupo hidroxilo, grupo nitro, grupo ciano, grupo amino, grupo mono- o di-alquilamino, grupo alcanoilo, grupo alquiltio, grupo tetrazolilo y grupo dihidrooxazolilo, en donde los grupo alquilo, alcoxilo, mono- o di-alquilamino, mono- o dialquilcarbamoilo, alcanoilo y alquiltio son opcionalmente sustituidos por un sustituyente(s) independientemente seleccionado del átomo halógeno, y grupo hidroxilo, alcoxilo, amino, morfolinilo, piperidinilo, pirrolidinilo, piperazinilo, alquilpiperazinilo y alcanoilpiperazinilo.

6. Un compuesto de acuerdo con la reivindicación 5, caracterizado por que el "anillo monocíclico aromático que opcionalmente contiene 1 a 3 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno son un grupo fenilo, un grupo piridilo, un grupo pirimidinilo, un grupo furilo o un grupo tienilo; y grupo heterocíclico saturado o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxígeno, azufre y nitrógeno es grupo pirimidinilo, grupo piridilo, grupo triazolilo, grupo tetrazolilo, grupo oxadiazolilo, grupo dihidropirimidinilo, grupo pirazinilo, grupo tiazolilo, grupo oxazolilo, grupo imidazolilo, grupo dihidrooxazinilo, grupo dihidropirazinilo o grupo pyrazolilo.

7. Un compuesto de acuerdo con la reivindicación 6,

caracterizado por que R^1 es un átomo de hidrógeno; un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo alquiltio, grupo alquilsulfonilo, grupo alquenilo, grupo amino, grupo mono- o di-alquilamino, grupo tetrazolilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo (dicho grupo mono- o di-alquilcarbamoilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo y grupo alcoxicarbonilo), grupo alcanoilamino (dicho grupo alcanoilamino es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo hidroxilo y átomo halógeno), átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo; grupo amino, grupo mono- o dialquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo

carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o dialquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo morfolinilo opcionalmente sustituido por grupo oxo, grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, grupo amino, grupo mono ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo carboxialcoxilo, grupo alcoxicarbonilalcoxilo), grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), y grupo pirimidinilo (dicho grupo pirimidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo carboxialcoxilo, grupo

alcoxicarbonilalcoxilo); grupo dihidrooxazolilo opcionalmente sustituido por 1 a 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; o un grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- ó di-alquilamino, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo) grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo);

R^2 es un grupo alquilo;

R^3 es un átomo de hidrógeno;

R^4 es un grupo alquileno;

R^5 es un grupo heterocíclico seleccionado del grupo pirimidinilo, grupo piridilo, grupo triazolilo, grupo tetrazolilo, grupo oxadiazolilo, grupo dihidropirimidinilo, grupo pirazinilo, grupo tiazolilo, grupo oxazolilo, grupo

imidazolilo, grupo dihidrooxazinilo, grupan pirazolilo y grupo dihidropirazinilo, en donde dicho grupo heterocíclico es sustituido por 1 a 4 sustituyentes seleccionado de los grupos siguientes, o 1 a 4 sustituyentes seleccionados de los grupos siguientes y grupo oxo:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo alquilo C_{3-10};

grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo mono- o di-alquilcarbamoilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo fenilo, carboxilo o hidroxilo), grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino opcionalmente sustituido por grupo carboxilo o alcoxilo, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo dioxolanilo opcionalmente sustituido por grupo alquilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo pirrolidinilo

opcionalmente sustituido por grupo alcoxicarbonila..quilo o carboxialquilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo morfolinilo, y grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo;

grupo alquenilo opcionalmente sustituido por un grupo seleccionado del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo benciloxicarbonilo, y grupo tetrazolilo;

grupo alqueniloxilo opcionalmente sustituido por grupo carboxilo;

grupo alcoxilo C_{3-10};

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo; grupo carboxilo, grupo alcoxicarbonilo, grupo tetrazolilo, grupo caxbamoilo, grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo hidroxilo, grupo alcoxilo opcionalmente sustituido por grupo carboxilo o hidroxilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo aminosulfonilo, grupo amino, grupo mono- o di-alquilamino sustituido por grupo carboxilo o alcoxilo. grupo

mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo cicloalquilo opcionalmente sustituido por grupo carboximetilo, grupo oxiranilo, grupo fenilo opcionalmente sustituido por grupo alcoxilo o carboxilo, grupo morfolinilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo pirrolidinilo opcionalmente sustituido por alcoxicaxbonilalquilo o carboxialquilo, grupo pirrolidinilo sustituido por grupo oxo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicaxbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilalquilo o carboxialquilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo, grupo pirimidinilo, grupo piridilo, grupo dioxolanilo opcionalmente sustituido por grupo alquilo, grupo oxadiazolilo opcionalmente sustituido por grupo oxo, grupo oxatiadiazolilo opcionalmente sustituido por grupo oxo, grupo pirrolidinilcarbonilo opcionalmente sustituido por grupo carboxilo, grupo piperidiniloxilo opcionalmente sustituido por grupo alquilo, y grupo morfolinilcarbonilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo fenilo;

grupo carbamoilo;

grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por un grupo seleccionado del grupo carboxilo,

grupo morfolinilo y grupo alcoxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo y grupo mono- o di-alquilcarbamoilo;

grupo alquilsulfinilo;

grupo alquilsulfonilo opcionalmente sustituido por un grupo seleccionado del grupo hidroxilo, carboxilo y grupo mono- o di-alquilcarbamoilo;

grupo amino;

grupo mono- o di-alquilamino opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino y grupo morfolinilo;

grupo alcanoilamino opcionalmente sustituido por un grupo seleccionado de grupo hidroxilo, grupo alcoxilo, grupo carboxilo y grupo amino;

grupo mono- o di-alquilureido opcionalmente sustituido por grupo alcoxilo;

grupo morfolinilcarbonilamino;

grupo sulfamoilo;

grupo mono- o di-alquilsulfamoilo;

grupo morfolinilo opcionalmente sustituido por un grupo seleccionado del grupo oxo y grupo carboxilo;

grupo tiomorfolinilo opcionalmente oxidado;

grupo piperazinilo opcionalmente sustituido por un grupo seleccionado del grupo ciano, grupo alquilo, grupo hidroxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialquilo, grupo alcanoilo, grupo hidroxialcanoilo, grupo alcoxialcanoilo, grupo benciloxicarbonilo, grupo mono- o di-alquilcarbamoilo, grupo mono- o di-alquilsulfamoilo, grupo alquilsulfonilo y grupo tetrazolilo;

grupo piperidinilo opcionalmente sustituido por un grupo seleccionado del grupo carboxilo, grupo hidroxilo, grupo oxo, grupo alquilo, grupo hidroxialquilo, grupo carboxialquilo, grupo alcanoilo, grupo alcoxilo, grupo fenilalcoxilo, grupo alcoxicarbonilo, y grupo alcoxicarbonilalquilo;

grupo pirrolidinilo opcionalmente sustituido por un grupo seleccionado del grupo oxo, grupo carboxilo, grupo alcanoilo y grupo mono- o di-alquilamino;

grupo pirrolinilo opcionalmente sustituido por grupo oxo;

grupo hexahidrodiazepinilo opcionalmente sustituido por grupo alcanoilo;

grupo diazolidinilo opcionalmente sustituido por grupo oxo;

grupo dioxolanilo opcionalmente sustituido por grupo alquilo;

grupo piridilo opcionalmente sustituido por grupo carboxilo, grupo hidroxilo o grupo hidroxialquilo (dicho

grupo piridilo además es opcionalmente oxidado);

grupo tetrazolilo sustituido por grupo hidroxilo o grupo alquilo que es opcionalmente sustituido por grupo morfolinilo;

grupo dihidrooxadiazolilo opcionalmente sustituido por grupo oxo;

grupo dihidroimidazolilo;

grupo dihidrooxazolilo;

grupo oxazolidinilo opcionalmente sustituido por grupo oxo;

grupo tetrahidropiridilo opcionalmente sustituido por grupo bencilo;

grupo pirimidinilo;

grupo tetrahidropiranilo;

grupo piperidiniloxilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo carboxilo, grupo carboxialquilo y grupo alcanoilo;

grupo pirrolidiniloxilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo carboxilo, grupo carboxialquilo y grupo alcanoilo;

grupo tetrahidropiraniloxilo;

grupo tetrahidrofuraniloxilo;

grupo tianiloxilo opcionalmente oxidado;

grupo morfolinilcarbonilo;

grupo piperazinilcarbonilo opcionalmente sustituido por

un grupo seleccionado del grupo alcanoilo y grupo alquilo; y

grupo pirrolidinilcarbonilo;

R^6 y R^9 cada uno es un átomo de hidrógeno;

R^7 y R^8 es independientemente un átomo de hidrógeno, un grupo alquilo opcionalmente sustituido por átomo halógeno, un grupo alcoxilo, un grupo mono- o di-alquilamino o átomo halógeno; o

R^7 y R^8 se combinan en los extremos para formar un grupo alquilendioxilo; y

R^{10} es un grupo fenilo o piridilo cuyo grupo fenilo o piridilo es opcionalmente sustituido por 1 a 4 sustituyentes seleccionados de grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, grupo hidroxilo, átomo halógeno, grupo ciano, grupo amino y grupo mono- o di-alquilamino.

8. Un compuesto de acuerdo con la reivindicación 7, caracterizado por que R^1 es un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo y grupo alcoxicarbonilo), grupo alquenilo, átomo halógeno, grupo cicloalquilo (dicho grupo

cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); y grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); o un grupo dihidrooxazolilo opcionalmente sustituido por 1 o 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxiloalquilo;

R^5 es un grupo pirimidinilo, un grupo piridilo, un grupo triazolilo, un grupo tetrazolilo, un grupo oxadiazolilo, un

grupo dihidropirimidinilo, un grupo pirazinilo, un grupo tiazolilo, un grupo oxazolilo, un grupo dihidrooxazinilo, un grupo pirazolilo o un grupo dihidropirazinilo, siendo dicho grupo sustituido por 1 a 4 sustituyentes seleccionados de los grupos siguientes:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo opcionalmente sustituido por grupo carboxilo o hidroxilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o dialquilsulfamoilamino, grupo mono- o di-alquilureido sustituido opcionalmente por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alquenilo opcionalmente sustituido por grupo carboxilo, grupo ciano o grupo benciloxicarbonilo;

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo opcionalmente sustituido por grupo carboxilo o hidroxilo, grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o dialquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o grupo carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo fenilo; grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo carboxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio;

grupo alquilsulfonilo opcionalmente sustituido por grupo carboxilo;

grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono- o di-alquilamino o grupo morfolinilo;

grupo mono- o di-alquilsulfamoilo; grupo morfolinilo;

grupo tiomorfolinilo opcionalmente oxidado;

grupo piperazinilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoílo y grupo hidroxialcanoilo;

grupo piperidinilo opcionalmente sustituido por un grupo seleccionado del grupo carboxilo, grupo alquilo y grupo alcoxicarbonilo;

grupo dioxolanilo opcionalmente sustituido por grupo alquilo;

grupo tetrazolilo opcionalmente sustituido por grupo alquilo, grupo hidroxialquilo o grupo morfolinilalquilo;

grupo dihidrooxadiazolilo opcionalmente sustituido por grupo oxo;

grupo pirimidinilo; o

grupo tetrahidropiranilo; y

R^{10} es un grupo fenilo o piridilo., cuyo grupo fenilo o piridilo es opcionalmente sustituido por 1 a 4 sustituyentes seleccionados de grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, grupo hidroxilo, átomo halógeno, grupo ciano, grupo amino y grupo mono- o di-

alquilamino.

9. Un compuesto de acuerdo con la reivindicación 1, caracterizado por que R^1 es un átomo de hidrógeno; un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionado del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo alquiltio, grupo alquilsulfonilo, grupo alquenilo, grupo amino, grupo mono- o di-alquilamino, grupo tetrazolilo, grupo carbamoilo, grupo mono- o di-alquilcarbamoilo (dicho grupo mono- o di-alquilcarbamoilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo y grupo alcoxicarbonilo), grupo alcanoilamino (dicho grupo alcanoilamino es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo hidroxilo y átomo halógeno), átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- o di-alquilamino, átomo

halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo morfolinilo opcionalmente sustituido por grupo oxo, grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo hidroxilo, grupo amino, grupo mono- ó di-alquilamino, átomo halógeno, grupo oxo, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo), y grupo pirimidinilo (dicho grupo pirimidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente

seleccionados del grupo carboxialquilo, grupo alcoxicarbonilalquilo, grupo carboxialcoxilo y grupo alcoxicarbonilalcoxilo); un grupo carbamoilo opcionalmente sustituido por grupo alcoxilo; grupo dihidrooxazolilo opcionalmente sustituido por 1 a 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; grupo dihidroimidazolilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; grupo dihidrooxazinilo opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo alquilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxialquilo; grupo mono- o di-alquilcarbamoilo sustituido por 1 a 5 sustituyentes independientemente seleccionados del átomo halógeno, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo amino, grupo mono- o di-alquilamino grupo, grupo morfolinilo, grupo piridilo, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino

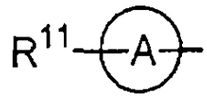
y grupo hidroxilo) y grupo fenilo (dicho grupo fenilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo amino y grupo hidroxilo);

R^2 es un grupo alquilo;

R^3 es un átomo de hidrógeno;

R^4 es un grupo alquileno;

R^5 es un grupo de la fórmula:



en donde el anillo A es un grupo heterociclico saturado o no saturado de 5 a 8 miembros que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno,

R^{11} es un grupo seleccionado de los grupos siguientes:

grupo ciano;

grupo nitro;

grupo carboxilo;

grupo sulfo;

grupo alquilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo

fenilo, hidroxilo o carboxilo), grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- ó di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alquenilo opcionalmente sustituido por grupo carboxilo, grupo ciano o grupo benciloxicarbonilo;

grupo alcoxilo sustituido por un grupo seleccionado del átomo halógeno, grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por grupo fenilo, hidroxilo o carboxilo), grupo alcanoiloxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- ó di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o dialquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente

sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperidinilo opcionalmente sustituido por grupo alcoxicarbonilo o carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo, grupo hexahidroazepinilo y grupo morfolinilo;

grupo alcoxicarbonilo opcionalmente sustituido por grupo fenilo;

grupo mono- o di-alquilcarbamoilo opcionalmente sustituido por grupo carboxilo;

grupo hidroxicarbamimidoilo;

grupo alquiltio;

grupo alquilsulfinilo;

grupo alquilsulfonilo opcionalmente sustituido por grupo carboxilo;

grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo mono ó di-alquilamino o grupo morfolinilo;

grupo mono- o di-alquilsulfamoilo;

grupo morfolinilo;

grupo tiomorfolinilo opcionalmente oxidado;

grupo piperazinilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo;

grupo pirrolidinilo opcionalmente sustituido por grupo

carboxilo, grupo carboxialquilo, grupo alquilo, grupo alcoxicarbonilo o grupo alcoxicarbonilalquilo;

grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo carboxialquilo, grupo alquilo, grupo alcoxicarbonilo o grupo alcoxicarbonilalquilo;

grupo dioxolanilo opcionalmente sustituido por grupo alquilo;

grupo tetrazolilo opcionalmente sustituido por grupo alquilo, grupo hidroxialquilo o grupo morfolinilalquilo;

grupo dihidrooxadiazolilo opcionalmente sustituido por grupo oxo;

grupo pirimidinilo; o

grupo tetrahidropiranilo;

R^6 y R^9 cada uno es un átomo de hidrógeno;

R^7 y R^8 son independientemente un átomo de hidrógeno, un grupo alquilo opcionalmente sustituidos por el átomo halógeno, grupo alcoxilo, o grupo mono- o di-alquilamino; o se combinan en los extremos para formar un grupo alquilendioxilo; y

R^{10} es un grupo fenilo o piridilo, cuyo grupo fenilo o piridilo es opcionalmente sustituido por 1 a 4 sustituyentes seleccionados del grupo alquilo opcionalmente sustiuido por átomo halógeno, grupo alcoxilo, grupo hidroxilo, átomo halógeno, grupo ciano, grupo amino y grupo mono- o di-alquilamino.

10. Un compuesto de acuerdo con la reivindicación 9,

caracterizado por que el anillo A es un grupo pirimidinilo, un grupo piridilo, un grupo triazolilo, un grupo tetrazolilo, un grupo oxadiazolilo, un grupo dihidropirimidinilo, un grupo pirazinilo, un grupo tiazolilo, un grupo oxazolilo, un grupo dihidrooxazinilo, un grupo imidazolilo, un grupo pirazolilo, o un grupo dihidropirazinilo.

11. Un compuesto de acuerdo con la reivindicación 10, caracterizado por que el anillo A es un grupo pirimidinilo, un grupo piridilo, un grupo tetrazolilo, un grupo oxadiazolilo, un grupo pirazinilo, un grupo tiazolilo o un grupo oxazolilo; y

R^{11} es un grupo carboxilo; un grupo ciano; un grupo nitro; un grupo alquilo sustituido por un grupo seleccionado de grupo hidroxilo, grupo ciano, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo, grupo hidroxialcoxilo, grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- ó di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o dialquilureido opcionalmente sustituido por morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y morfolinilo; un grupo alquenilo opcionalmente sustituido por

grupo carboxilo; un grupo alcoxilo sustituido por un grupo seleccionado de grupo hidroxilo, grupo ciano, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo, grupo hidroxialcoxilo, grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido sustituido opcionalmente por grupo morfolinilo, grupo oxiranilo, grupo di-alquildioxolanilo, grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y grupo morfolinilo; un grupo alcoxicarbonilo; un grupo hidroxicarbarnimidoilo; grupo alquiltio; grupo alquilsulfonilo opcionalmente sustituido por grupo carboxilo; un grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo; grupo carboxilo, grupo alcoxilo o grupo mono- o di-alquilamino; un grupo morfolinilo; grupo tiomorfolinilo opcionalmente oxidado; grupo piperazinilo opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo; grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo alquil carboxialquilo o grupo alcoxicarbonilo; un grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo alquilo, grupo carboxialquilo o, grupo alcoxicarbonilo;

un grupo tetrazolilo opcionalmente sustituido por grupo alquilo, grupo hidroxialquilo, o grupo morfolinilalquilo; un grupo oxodihidrooxadiazolilo; un grupo pirimidinilo; o un grupo tetrahidropiranilo.

12. Un compuesto de acuerdo con la reivindicacion 11, caracterizado por que R^1 es un grupo alcoxicarbonilo opcionalmente sustituido por 1 a 5 sustituyentes independientemente seleccionados de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo (dicho grupo alcoxilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo y grupo alcoxicarbonilo), grupo alquenilo, átomo halógeno, grupo cicloalquilo (dicho grupo cicloalquilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo), grupo fenilo (dicho grupo fenilo es opcionalmente sustituido, por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); grupo piperidinilo (dicho grupo piperidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo

carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); y grupo pirrolidinilo (dicho grupo pirrolidinilo es opcionalmente sustituido por 1 a 3 sustituyentes independientemente seleccionados de grupo hidroxilo, átomo halógeno, grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo y grupo alcoxicarbonilalquilo); o un grupo dihidrooxazolilo opcionalmente sustituido por 1 o 2 sustituyentes independientemente seleccionados del grupo carboxilo, grupo alcoxicarbonilo, grupo carboxialquilo, grupo alcoxicarbonilalquilo y grupo hidroxiloalquilo;

R^{10} es un grupo fenilo sustituido por 1 a 3 sustituyentes seleccionados de grupo alquilo opcionalmente sustituido por átomo halógeno, grupo alcoxilo, átomo halógeno y grupo ciano;

el anillo A es un grupo pirimidinilo, un grupo piridilo, un grupo tetrazolilo, un grupo oxadiazolilo o un grupo tiazolilo; y

R^{11} es un grupo carboxilo; un grupo ciano; un grupo nitro; un grupo alquilo sustituido por un grupo seleccionado de grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo; grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o di-alquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo

oxiranilo, grupo di-alquildioxolanilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y grupo morfolinilo; un grupo alquenilo opcionalmente sustituido por grupo carboxilo; un grupo alcoxilo sustituido por un grupo seleccionado del grupo ciano, grupo hidroxilo, grupo carboxilo, grupo alcoxicarbonilo, grupo alcoxilo, grupo fenilalcoxilo, grupo carboxialcoxilo, grupo alquiltio, grupo alquilsulfonilo, grupo alquilsulfinilo, grupo amino, grupo mono- o di-alquilamino, grupo mono- o dialquilsulfamoilamino, grupo mono- o di-alquilureido opcionalmente sustituido por grupo morfolinilo, grupo oxiranilo, grupo dialquildioxolanilo, grupo piperazinilo opcionalmente sustituido por grupo alquilo y grupo morfolinilo; un grupo hidroxicarbamimidoilo; un grupo alquiltio; un grupo alquilsulfonilo opcionalmente sustituido por grupo alcoxicarbonilo; un grupo mono- o di-alquilamino opcionalmente sustituido por grupo hidroxilo, grupo carboxilo o grupo alcoxilo; un grupo morfolinilo; grupo tiomorfolinilo opcionalmente oxidado; un grupo piperazinil opcionalmente sustituido por un grupo seleccionado del grupo alquilo, grupo alcanoilo y grupo hidroxialcanoilo; un grupo pirrolidinilo opcionalmente sustituido por grupo carboxilo, grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilo; un grupo piperidinilo opcionalmente sustituido por grupo carboxilo, grupo alquilo, grupo carboxialquilo o grupo alcoxicarbonilo; un grupo tetrazolilo opcionalmente sustituido por grupo

alquilo, grupo hidroxialquilo, o grupo morfolinilalquilo; un grupo oxodihidrooxadiazolilo; un grupo pirimidinilo; o un grupo tetrahidropiranilo.

13. Un compuesto de acuerdo con la reivindicación 12, caracterizado por que R^1 es un grupo alcoxicarbonilo opcionalmente sustituido por 1 o 5 sustituyentes independientemente seleccionados de grupo carboxilo, grupo alcoxicarbonilo, átomo halógeno, grupo hidroxilo y grupo cicloalquilo;

R^{10} es un grupo fenilo sustituido por 1 a 3 sustituyentes seleccionados del grupo ciano, grupo alquilo opcionalmente sustituido por átomo halógeno y grupo alcoxilo;

el anillo A es un grupo pirimidinilo, un grupo piridilo, un grupo tetrazolilo o un grupo oxadiazolilo;

R^{11} es un grupo carboxilo; un grupo alquilo sustituido por grupo hidroxilo, grupo carboxilo, grupo alcoxilo o grupo alquilsulfonilo; un grupo alquenilo opcionalmente sustituido por grupo carboxilo; un grupo alcoxilo sustituido por grupo carboxilo, grupo ciano, grupo hidroxilo, grupo alcoxilo, grupo alquiltio o grupo alquilsulfonilo; un grupo mono- o di-alquilamino opcionalmente sustituido por grupo carboxilo o grupo alcoxilo; un grupo morfolinilo; un grupo piperidinilo sustituido por grupo carboxilo; o un grupo tetrazolilo sustituido por grupo hidroxialquilo;

R^7 es un grupo alquilo opcionalmente sustituido por átomo

halógeno, grupo alcoxilo, o grupo mono- o di-alquilamino; y

R^8 es un átomo de hidrógeno.

14. Un compuesto de acuerdo con la reivindicación 13, caracterizado por que R^1 es un grupo etoxicarbonilo, un grupo hidroxietoxicarbonilo, un grupo 2-fluoroetoxicarbonilo, un grupo 2,2-difluoroetoxicarbonilo o un grupo 2,2,2-trifluoroetoxicarbonilo; R^2 es un grupo etilo; R^{10} es un grupo fenilo sustituido por 1 a 2 sustituyentes seleccionados del grupo ciano, grupo trifluorometilo y grupo metoxilo; y R^7 es un grupo trifluorometilo o un grupo metoxilo.

15. Un compuesto de acuerdo con la reivindicacion 13, caracterizado por que R^1 es un grupo carboxi(C_{2-10} alcoxi)carbonilo o un grupo alcoxicarbonil(C_{2-10} alcoxi)carbonilo; R^2 es un grupo etilo; R^{10} es grupo fenilo sustituido por 1 ó 2 sustituyentes seleccionados de grupo ciano, grupo trifluorometilo y grupo metoxilo; y R^7 es un grupo trifluorometilo o un grupo metoxilo.

16. Un compuesto caracterizado por que es seleccionado de los compuestos siguientes o una sal farmacéuticamente aceptable del mismo.

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-[5-{[metil-(2-metoxietil)amino}pirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-carboxipirimidin-2-il)}amino-2-etil-6trifluorometil-3,4-dihidro-2H-quinolina-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-carboxietil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-{5-[2-(2-hidroxietil)-2H-tetrazol-5-il]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3,5-Dimetoxibencil)-[5-(morfolin-4-il)pirimidin-2il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolinelcarboxílico;

Etil éster de ácido (2R,4S)-4-{(3,5-Dicianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluororrietil-3,4-dihidro-2H-quinolin-1-carboxílico.;

Etil éster de ácido (2R,4S)-4-{(3-Cianobencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-{5-[2-(2-hidroxietil)-2H-tetrazol-5-il]pirimidin-2-il})amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2-hidroxietil)-2H-tetrazol-5-il]pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[2-(2-metansulfoniletil)-2H-tetrazol-5-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Hidroxiletil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H--quinolin-1-

carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirmidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico.;

Etil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(2-carboxietil)-pirimidin-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-{[metil-(2-carboxietil)-amino}pirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-([3,5-Bis(trifluorometil)bencil]-{5-[3-(tetrazol-5-il)propoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxibutoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-[5-(5-carboxipentiloxi)pirimicin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-carboxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboximetilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxibutoxi)piridin2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(4-carboxibutoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-

il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-dimetilamino-3,4dihidro-2H-quinolin-1-carboxílico;

2,2,2-Trifluoroetil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2,2,2-trifluoroetil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2,2,2-trifluoroetil éster de ácido (2R,4S)-4-{(3-Ciano-5-trifluorometilbencil)-[5-(3-carboxipropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4dihidro-2H-quinolin-1-carboxílico;

2-Hidroxiletil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-carboxipiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-

2H-quinolin-1-carboxílico.

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico; ó

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico.

17. Un compuesto caracterizado por que es seleccionado

de los siguientes compuestos o una sal farmacéuticamente aceptable del mismo:

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{ 3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

5-Carboxipentil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-dimetilaminopirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolir-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{(3-ciano-5-

trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-

il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-hidroxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(3-cianopropoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-

carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-dimetilaminopiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)piridin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-

Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

3-Carboxipropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

4-Carboxibutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)piridin-2-

il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

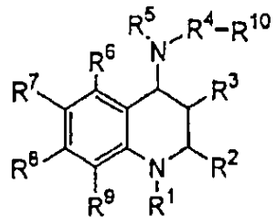
4-Carboxibutil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxi-2-metilpropil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(morfolin-4-il)piridin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico;

2-Carboxietil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6,7-etilendioxi-3,4-dihidro-2H-quinolin-1-carboxílico; ó

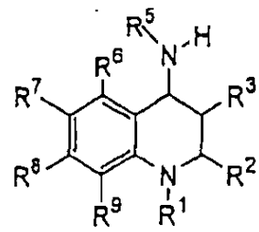
2-Carboxietil éster de ácido (2R,4S)-4-{(3-ciano-5-trifluorometilbencil)-[5-(2-metoxietoxi)pirimidin-2-il]}amino-2-etil-6,7-etilendioxi-3,4-dihidro-2H-quinolin-1-carboxílico.

18. Un procedimiento para preparar un derivado tetrahidroquinolina de la fórmula (I):



(I)

en donde los símbolos R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 y R^{10} tienen el mismo significado como el definido en la reivindicación 1, caracterizado por que comprende condensar un compuesto de la fórmula (II):



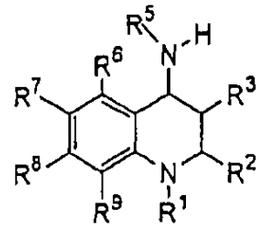
(II)

en donde cada símbolo tiene el mismo significado como el definido precedentemente con un compuesto de la fórmula (III):

$$R^{10}-R^4-Z^1 \qquad (III)$$

en donde Z^1 es un grupo de partida y los otros símbolos tienen el mismo significando como el definido anteriormente.

19. Un compuesto de la fórmula (II):

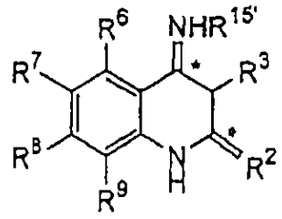


(II)

Caracterizado por que los símbolos R^1, R^2, R^3, R^5, R^6, R^7, R^8 y

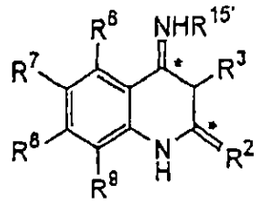
R^9 tienen el mismo significado como el definido en la reivindicación 1, o una sal del mismo.

20. Una mezcla diastereomérica caracterizada por que posee la fórmula (XIII-a):

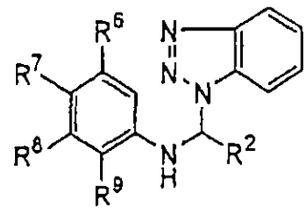

(XIII-a)

en donde $R^{15'}$ es un grupo protector ópticamente activo para el grupo amino y los símbolos R^2, R^3, R^6, R^7, R^8 y R^9 tienen el mismo significado como el definido en la reivindicación 1, o una sal del mismo.

21. Un procedimiento para preparar una mezcla de diastereómeros caracterizado por que es una mezcla de la fórmula (XIII-a):


(XIII-a)

en donde $R^{15'}$ es un grupo protector ópticamente activo para el grupo amino ópticamente activo y los símbolos R^2, R^3, R^6, R^7, R^8 y R^9 tienen el mismo significado como el definido en la reivindicación 1 que comprende hacer reaccionar un compuesto de la fórmula (XV):



(XV)

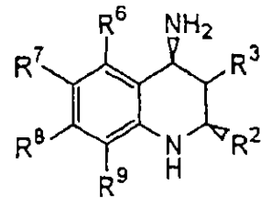
en donde cada símbolo posee el mismo significado como el definido precedentemente con un compuesto de fórmula (XIV-a):



(XIV-a)

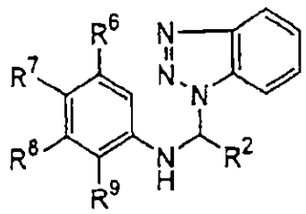
en donde cada símbolo posee el mismo significado como el definido precedentemente.

22. Un procedimiento para preparar un compuesto ópticamente activo caracterizado por que posee la fórmula (XIII-b)



(XIII-b)

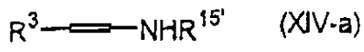
en donde los símbolos R^2, R^3, R^6, R^7, R^8 y R^9 tienen el mismo significado como el definido en la reivindicación 1, que comprende hacer reaccionar un compuesto de la fórmula (XV):



(XV)

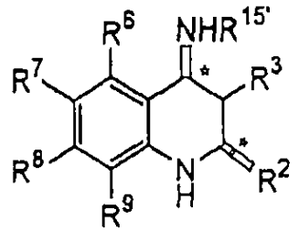
en donde cada símbolo posee el mismo significado como el definido precedentemente con un compuesto de la fórmula (XIV-

a):



(XIV-a)

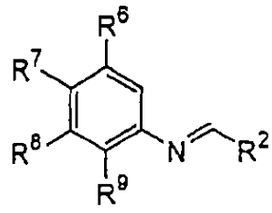
en donde $R^{15'}$ es un grupo protector ópticamente activo para un grupo amino y R^3 tiene el mismo significado como el definido precedentemente, resolviéndo la mezcla de diastereómeros resultante de la fórmula (XIII-a):



(XIII-a)

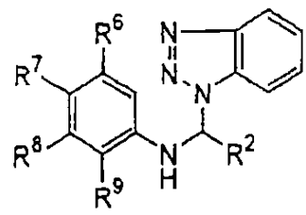
en donde cada símbolo posee el mismo significado como el definido precedentemente, y eliminar el grupo protector ópticamente activo para grupo amino.

23. Un procedimiento de acuerdo con la reivindicación 21 ó 22, caracterizado por que un compuesto de la fórmula (XVIII):



(XVIII)

en donde los símbolos R^2, R^6, R^7, R^8 y R^9 poseen el mismo significado como el definido en la reivindicación 1 es utilizado en lugar del compuesto (XV):



(XV)

en donde cada símbolo posee el mismo significado como el definido precedentemente.

24. Una composición farmacéutica, caracterizada por que comprende como un ingrediente activo un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 17, o una sal farmacéuticamente aceptable del mismo.

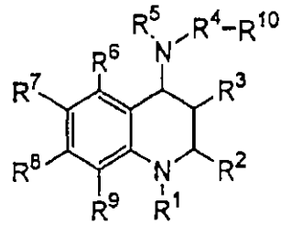
25. Un método caracterizado por que se aplica para profilaxis o tratamiento de arteriosclerosis, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesteremia, hipertrigliceridemia, hipercolesteremia familiar, enfermedades cardiovasculares, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, lesión de reperfusión, restenosis después de angioplastia, hipertensión, infarto cerebral, accidente cerebral, diabetes, complicación vascular de diabetes, enfermedades trombóticas, obesidad o endotoxemia que comprende administrar una cantidad eficaz de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 17, o una sal farmacéuticamente aceptable del mismo, a un paciente que necesita del mismo.

26. Una aplicación de un compuesto de acuerdo con

cualquiera de las reivindicaciones 1 a 17, o una sal farmacéuticamente aceptable de eso, caracterizado por que se indica en el tratamiento de pacientes que padecen arteriosclerosis, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesteremia, hipertrigliceridemia, hipercolesteremia familiar, enfermedades cardiovasculares, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, lesión de reperfusion, restenosis después de angioplastia, hipertensión, infarto cerebral, accidente cerebral, diabetes, complicación vascular de diabetes, enfermedades trombóticas, obesidad o endotoxemia.

RESUMEN

Un nuevo compuesto de la fórmula (I):



(I)

en donde R^1 es alcoxicarbonilo o lo similar, R^2 es alquilo o lo similar; R^3 es hidrógeno o lo similar; R^4 es alquileno o lo similar; R^5 es grupo heterocíclico opcionalmente sustituido; R^6, R^7, R^8 y R^9 son independientemente hidrógeno; alquilo, alcoxilo, o lo similar; R^{10} es anillo aromático opcionalmente sustituido, o lo similar; o una sal farmacéuticamente aceptable del mismo que posee una actividad inhibitoria contra proteína de transferencia de colesteril éster (CETP).

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 665083	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No PCT/JP2005/006894	International filing date *(day/month/year)* 01.04.2005	Priority date *(day/month/year)* 02.04.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07D491/04 C07D401/14 C07D401/04 A61K31/47 A61K31/4545 A61K31/444 A61K31/4439 A61P3/06

Applicant
TANABE SEIYAKU CO., LTD.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of 25 sheets, as follows.
      - ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70 16 and Section 607 of the Administrative Instructions).
      - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items

- ☒ Box No I Basis of the report
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- ☐ Box No VI Certain documents cited
- ☒ Box No VII Certain defects in the international application
- ☐ Box No VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.02.2006	10.07.2006

Name and mailing address of the international preliminary examining authority	Authorized officer
European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Tx. 523656 epmu d Fax +49 89 2399 - 4465	Schmid, A Telephone No +49 89 2399-8591

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No
PCT/JP2005/006894

Box No. I Basis of the report

1 With regard to the **language**, this report is based on

☒ the international application in the language in which it was filed

☐ a translation of the international application into , which is the language of a translation furnished for the purposes of.

- ☐ international search (under Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-87, 89-93, 95-104, 106-126, 128-147, 149, 152, 153, 156-164, 167, 169-171, 173-181, 184-188, 190-214, 217-229, 231-235, 238, 239, 242-254, 256-261, 263-265	as originally filed
88, 94, 105, 127, 148, 150, 151, 154, 155, 165, 166, 168, 172, 182, 183, 189, 215, 216, 230, 236, 237, 240, 241, 255, 262	received on 01.02.2006 with letter of 30.01.2006

Claims, Numbers

1-26	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2005/006894

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25.26

because:

☒ the said international application, or the said claims Nos. 25,26 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings, the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2005/006894

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No.	Claims	
Inventive step (IS)	Yes:	Claims	1-19,21-26
	No:	Claims	20
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations (Rule 70.7).

   see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2005/006894

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 25 and 26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

1) The examiner agrees to the reasoning as already established in the search report.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:

D1: WO 00/17165 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MAGNUS-ARYITEY, GEORGE, T) 30 March 2000 (2000-03-30)

D2: WO 00/17166 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MULARSKI, CHRISTIAN, JAME) 30 March 2000 (2000-03-30)

D3: FR-A-2 763 590 (SYNTHELABO) 27 November 1998 (1998-11-27)

D4: WO 98/38194 A (RHONE-POULENC RORER S.A; HARDY, JEAN-CLAUDE; BOUQUEREL, JEAN; NEMECEK,) 3 September 1998 (1998-09-03)

D5: WANG C ET AL: "Design of a high affinity peptidomimetic opioid agonist from peptide pharmacophore models" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 19, 6 October 1998 (1998-10-06), pages

2685-2688, XP004139601 ISSN: 0960-894X

D6: M. E. HICKS ET AL: "differential effect of the novel non-peptidic opioid 4-tyrosylamido-6-benzyl-1,2,3,4 tetrahydroquinoline (CGPM-9) on in vitro rat t lymphocyte and macrophage functions" LIFE SCIENCE, vol. 68, no. 24, 2001, pages 2685-2694, XP002354487

Invention 1:

1) The subject-matter of present claims 1-19, and 24-26 differs from the prior art represented by D1 and D2 essentially in the present substituent R5 (heterocyclic group) which is not possible in D1 and D2

Accordingly, the subject-matter of present claims 1-19 and 24-26 is novel pursuant to Article 33(2) PCT.

2) A skilled person looking for alternative compounds useful in the inhibition of CETP would surely not try to modify the known compounds just in the way as claimed in the present application with a reasonable expectation of success in order to obtain compounds with the desired activity as could be proved by the applicant on page 90, table.

Therefore, the subject-matter of invention 1 also involves an inventive step with regard to Article 33(3) PCT.

3) For the assessment of the present claims 25 and 26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Invention 2:

1) The documents D3-D6 (cf. specifications in the search report) disclose compounds falling under the general formula XIII-a since the present group R_{15} covers all the groups as disclosed in D3-D6.

However, since D3-D6 do not specifically disclose an **optically active** protecting group the subject-matter of present claim 20 is novel pursuant to Article 33(2) PCT.

The patentability of present claims 21-23 depends from claim 20, therefore the subject-matter of present claims 21-23 is also considered to be novel.

2) Although the subject-matter of present claim 20 has to be considered to be formally novel, it is quite clear to a person skilled in chemical synthesis to use an optically active group, if an optically active end product is required (which is the purpose of compounds XIII-a).

Accordingly, the subject-matter of present claim 20 is not inventive and does thus not meet the requirements of Article 33(3) PCT.

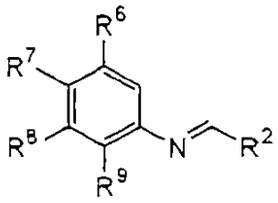
3) Present claim 21-23 concerns methods which general principle is not known from the prior art and cannot be derived therefrom.

Therefore, the subject-matter of present claims 21-23 involves an inventive step according to Article 33(3) PCT.

Re Item VII

Certain defects in the international application

1) D3-D6 which represent a relevant prior art should be referred to in the description in accordance to Rule 5(1)(a)(ii) PCT.



(XVIII)

This reaction can be carried out in the same manner as the reaction of a compound of the formula (XIV) with a compound of the formula (XV).

Additionally, respective substituents R^1, R^5, R^6, R^7, R^8 and R^9 can be converted into a desirable substituent in accordance with any one of processes from the PROCESS 4-(A) to (K) and from (1) to (58).

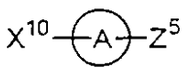
A compound of the formula (IV) can be prepared by condensing a compound of the formula (X) with a compound of the formula (III)

R^{10}-R^4-Z^1 (III)

wherein the symbols have the same meaning as defined above.

The condensation can be carried out in the same manner as described in WO00/17165 or the PROCESS 1 above.

A compound of the formula (IX) can be prepared by condensing a compound of the formula (IV) with a compound of the formula:



wherein Z^5 is a leaving group and the other symbols have the same meaning as defined above.

As the leaving group, a halogen atom including chlorine atom, bromine atom, iodine atom; a substituted sulfonyloxy group including methanesulfonyloxy group, p-toluenesulfonyloxy group, trifluoromethanesulfonyloxy group can be preferably used.

The condensation can be carried out in the same manner as the one of the said compound (X) with the compound (XI).

Additionally, the compound of the formula (IX) wherein Ring A is a tetrazolyl group and X^{10} is a hydrogen atom can be prepared by reacting a compound of the formula (V) with an alkyl metal azide. The reaction can

mixture is allowed to cool to room temperature, and the reaction solution is concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 5:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-dimethylaminopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (18 mg). MS (m/z): 664 $[M+H]^+$

Example 9

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (600 mg) and 2-chloro-5-propylpyrimidine (1.5 g) are dissolved in 1,3-dimethylimidazolidinone (10 ml), and the mixture is stirred at 135°C for 72 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 6:1→4:1) to give (2R,4S)-2-ethyl-4-(5-propylpyrimidin-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (250 mg). MS (m/z): 437 $[M+H]^+$

(2) (2R,4S)-2-Ethyl-4-(5-propylpyrimidin-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (240 mg) and 3,5-bis(trifluoromethyl)benzyl bromide (337 mg) are dissolved in N,N-dimethylformamide (3 ml), and thereto is added sodium hydride (62.7 %, 32 mg) at room temperature, and the mixture is stirred at the same temperature for 2 hours. To the reaction solution is added acetic acid, and water and ethyl acetate are added thereto. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 49:1→7:3) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-propylpyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (130 mg). MS (m/z): 663 $[M+H]^+$

reaction solution is added acetic acid, and thereto are added water and ethyl acetate. The organic layer is washed again with water, and the organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 49:1→13:7) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-nitropyridin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (650 mg). MS (m/z): 665 $[M+H]^+$

Example 28

(1) (2R,4S)-4-[3,5-Bis(trifluoromethyl)benzyl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (600 mg) is dissolved in ethanol (5.0 ml), and thereto are added cyanogen bromide (129 mg) and sodium hydrogen carbonate (283 mg), and the mixture is stirred at room temperature for 23 hours and 15 minutes. Distilled warer is added to the mixture, and the mixture is extracted with ether. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-cyano}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (581 mg). MS (m/z): 585 $[M+H_2O]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-cyano}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (50 mg) is dissolved in N,N-dimethylformamide (1 ml), and thereto are added sodium azide (57.2 mg) and ammonium chloride (47.1 mg), and the mixture is stirred at 100°C for 16.5 hours. The mixture is allowed to cool to room temperature, and thereto is added distilled water, and the mixture is extracted with ethyl acetate. The organic layer is dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; chloroform:methanol =

mixture is stirred at 100°C for 3 hours. The reaction solution is cooled to room temperature, and thereto are added an aqueous citric acid solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-2-ethyl-4-(5-nitorthiazol-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (148 mg). MS (m/z): 445 $[M+H]^+$

(2) (2R,4S)-2-Ethyl-4-(5-nitrothiazol-2-yl)amino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (133 mg) and 3,5-bis(trifluoromethyl)benzyl bromide (179 mg) are dissolved in tetrahydrofuran (3 ml), and thereto is added sodium hydride (62.7 %, 34 mg), and the mixture is stirred at room temperature overnight. To the reaction solution is added acetic acid, and thereto are added water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→2:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-nitrothiazol-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (58 mg). MS (m/z): 671 $[M+H]^+$

Example 89

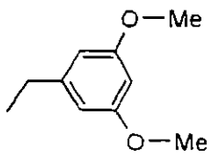
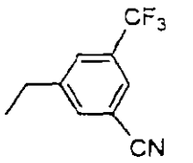
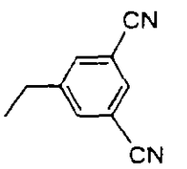
(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-cyano}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (327.9 mg) is dissolved in tetrahydrofuran (3 ml), and thereto is added sodium hydride (62.7 %, 13.9 mg). The mixture is stirred with ice-cooling under nitrogen atmosphere for one hour. To the reaction solution is slowly added dropwise a solution of 3-buten-1-ol (41.8 mg) in tetrahydrofuran (4 ml) under ice-cooling, and the mixture is stirred at room temperature for 29 hours. Distilled water is added under ice-cooling, and the mixture is extracted with ethyl acetate. The organic layer is dried over magnesium

(2) (2R,4S)-4-[(tert-Butoxycarbonyl)-(5-bromopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5 g) is dissolved in 1,4-dioxane (60 ml), and thereto are added acrylic acid benzyl ester (2.83 g), tris(dibenzylideneacetone)dipalladium (1.2 g), tri(tert-butyl)phosphonium tetrafluoroborate (760 mg), and N,N-dicyclohexylmethylamine (1.87 g). The mixture is stirred at room temperature under nitrogen atmosphere for 2.5 hours, and thereto is added a saturated aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{(tert-butoxycarbonyl)-[5-(2-benzyloxycarbonylvinyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.65 g). MS (m/z): 655 $[M+H]^+$

(3) (2R,4S)-4-{(tert-Butoxycarbonyl)-[5-(2-benzyloxycarbonylvinyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.65 g) is dissolved in methylene chloride (10 ml), and thereto is added trifluoroacetic acid (1 ml). The mixture is stirred at room temperature overnight, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-[5-(2-benzyloxycarbonyl-vinyl)pyrimidin-2-yl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.38 g). MS (m/z): 555 $[M+H]^+$

(4) (2R,4S)-4-[5-(2-Benzyloxycarbonylvinyl)pyrimidin-2-yl]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.41 g) is dissolved in N,N-dimethylformamide (30 ml), and thereto is added sodium hydride (62.7%, 360 mg) under ice-cooling. The mixture is stirred under ice-cooling for 30 minutes, and thereto is added 3,5-dibromobenzyl bromide (3 g). The mixture is stirred at room temperature

Table 20

Example	R^4-R^{10}	Physical properties, etc.
139		MS (m/z): 617 $[M+H]^+$
140		MS (m/z): 650 $[M+H]^+$
141		MS (m/z): 607 $[M+H]^+$

Example 142

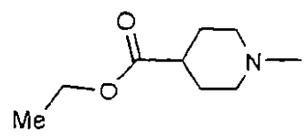
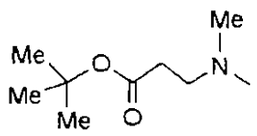
(2R,4S)-4-{[5-(2-Carboxyethyl)pyrimidin-2-yl]-(3,5-dimethoxybenzyl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (145 mg) and triethylamine (98 µl) are dissolved in tetrahydrofuran (3 ml), and thereto is added dropwise ethyl chlorocarbonate (67 µl) at 0°C. The mixture is stirred at the same temperature for 30 minutes, and thereto is added sodium borohydride (44 mg). The mixture is further stirred at the same temperature for 3 hours. To the reaction solution are added an aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{(3,5-dimethoxybenzyl)-[5-(3-hydroxypropyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (68 mg). MS (m/z): 603 $[M+H]^+$

Example 143

(2R,4S)-4-[(3,5-Dimethoxybenzyl)-(5-iodopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (302 mg) is dissolved in N,N-dimethylformamide (2.5 ml), and thereto are added tetrakis(triphenylphosphine)palladium (104 mg), pyrimidine-5-boronic acid (112 mg) and sodium carbonate (114 mg). The mixture is stirred at 100°C under nitrogen atmosphere for 4 hours. The mixture is allowed to cool to room temperature, and water is added thereto. The mixture is extracted with ethyl acetate, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 2:1) to give (2R,4S)-4-[([5,5']bipyrimidin-2-yl)-(3,5-dimethoxybenzyl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (106 mg). MS (m/z): 623 $[M+H]^+$

Example 144

(1) (2R,4S)-4-[(3,5-Dimethoxybenzyl)-(5-iodopyrimidin-2-yl)]amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.89 g) is dissolved in toluene (12 ml), and thereto are added benzyl alcohol (1.2 ml), copper(I) iodide (221 mg), cesium carbonate (1.89 g), and 1,10-phenanthroline (418 mg), and the mixture is stirred at 100°C for one day. To the reaction solution are added water and ethyl acetate, and the mixture is filtered through Celite™ to remove the insoluble materials. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is dissolved in toluene (12 ml), and thereto are added benzyl alcohol (0.3 ml), copper(I) iodide (221 mg), cesium carbonate (1.89 g), and 1,10-phenanthroline (418 mg). The mixture is stirred at 100°C for one day, and allowed to cool to room temperature. To the reaction solution are added water and ethyl acetate, and the mixture is filtered through Celite™ to

148		MS (m/z): 738 [M+H]+
149		MS (m/z): 740 [M+H]+

Example 150

(2R,4S)-4-{[5-(4-Benzyloxycarbonylpiperazin-1-yl)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.78 g) is dissolved in ethanol (50 ml), and thereto is added 10 % palladium-carbon (300 mg). The mixture is stirred at room temperature under hydrogen atmosphere for 3 hours. The catalyst (10 % palladium-carbon) is removed by filtration, and the filtrate is concentrated under reduced pressure, and the resulting residue is purified by column chromatography (NH-silica gel; hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(piperazin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (470 mg). MS (m/z): 667 [M+H]+

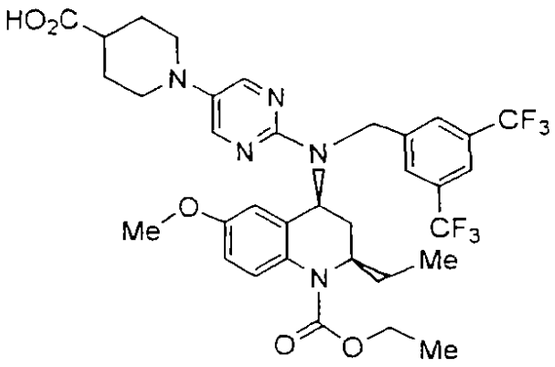
Example 151

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(piperazin-1-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (100 mg) and pyridine (18 µl) are dissolved in methylene chloride (1 ml), and thereto is added acetoxyacetic acid chloride (19.4 µl) at room temperature. The mixture is stirred overnight, and washed with a 1N hydrochloric acid. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by column chromatography (silica gel; hexane:ethyl acetate = 7:3→2:3) to give (2R,4S)-4-{[5-[4-(2-acetoxyacetyl)piperazin-1-yl]pyrimidin-2-yl}-[3,5-bis(trifluoromethyl)

benzyl])amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (110 mg). MS (m/z): 767 $[M+H]^+$

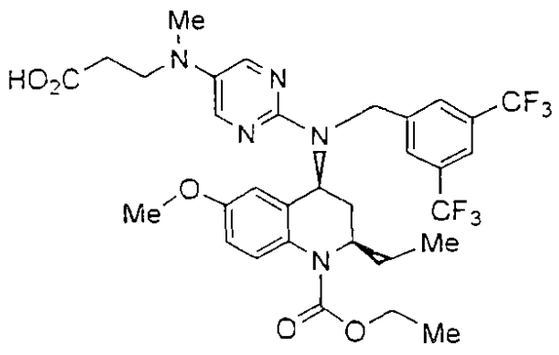
(2) (2R,4S)-4-({5-[4-(2-Acetoxyacetyl)piperazin-1-yl]pyrimidin-2-yl}-[3,5-bis(trifluoromethyl)benzyl])amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (87 mg) is dissolved in ethanol (1 ml), and thereto is added potassium carbonate (23 mg) at room temperature, and the mixture is stirred overnight. The insoluble materials are removed by filtration, and the filtrate is concentrated under reduced pressure to give (2R,4S)-4-([3,5-bis(trifluoromethyl)benzyl]-{5-[4-(2-hydroxyacetyl)piperazin-1-yl]pyrimidin-2-yl})amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (83 mg). MS (m/z): 725 $[M+H]^+$

Example 152



The corresponding starting compound is treated in a similar manner to Example 124 to give the compound of Example 152. MS (m/z): 710 $[M+H]^+$

Example 153



carbonate solution, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue (23 g) and 5-bromo-2-chloropyrimidine (29.3 g) are dissolved in 1,4-dioxane (100 ml), and thereto is added N,N-diisopropylethylamine (32 ml), and the mixture is refluxed overnight. The reaction solution is cooled to room temperature, and thereto are added water and diethyl ether, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 6:1→2:1) to give (2R*,4S*)-4-(5-bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (24.0 g). MS (m/z): 535/537 [M+H]+

(6) (2R*,4S*)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (13 g) is treated in a similar manner to Example 1-(2) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (20.6 g). MS (m/z): 761/763 [M+H]+

(7) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (18.3 g) is treated in a similar manner to Example 1-(3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-3,4-dihydro-6-trifluoromethyl-2H-quinoline-1-carboxylic acid benzyl ester (11.2 g). MS (m/z): 768 [M+H]+

(8) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (11.2 g) is treated in a similar manner to Example 150 to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-

dihydro-2H-quinoline (8.9 g). MS (m/z): 634 $[M+H]^+$

Example 174

(2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (500 mg) and triethylamine (132 µl) are dissolved in methylene chloride (5 ml), and thereto is added triphosgene (94 mg) at room temperature, and the mixture is stirred for one hour. The reaction solution is concentrated under reduced pressure, and the resulting residue is separated into ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (5 ml), and ethylene glycol (0.5 ml), triethylamine (295 ml) and 4-dimethylaminopyridine (26 mg) are added thereto. The mixture is stirred at room temperature overnight. The reaction solution is separated into ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 3:1→2:3) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-hydroxyethyl ester (430 mg). MS (m/z): 722 $[M+H]^+$

Example 175

(1) (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.28 g), 2-chloroxazole-4-carboxylic acid ethyl ester (1.44 g) and diisopropylethylamine (1.42 ml) are dissolved in 1,4-dioxane (10 ml), and the mixture is stirred at 130°C overnight. The reaction solution is cooled to room temperature, and water and ethyl acetate are added thereto. The organic layer is washed with a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure.

pressure. The resulting residue is dissolved in tetrahydrofuran (100 ml), and thereto is added dropwise a 30 % aqueous hydrogen peroxide solution (70 ml) under ice-cooling. One hour thereafter, a saturated aqueous sodium thiosulfate solution is added to the mixture, and the excess hydrogen peroxide is consumed. The mixture is separated into water and ethyl acetate. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 5:1→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (19.22 g). MS (m/z): 637 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (6.5 g) and 4-bromobutyric acid ethyl ester (2.19 g) are dissolved in N,N-dimethylformamide (50 ml), and thereto is added potassium carbonate (1.69 g), and the mixture is stirred at 45°C overnight. Ethyl acetate and water are added to the mixture, and the organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (6.52 g). MS (m/z): 751 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-ethoxycarbonylpropoxy)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (6.5 g) is dissolved in ethanol (65 ml), and thereto is added a 2N aqueous sodium hydroxide solution (13 ml). The mixture is stirred at room temperature overnight. The reaction solution is concentrated under reduced pressure, and to the residue are added ethyl

hydrochloric acid and ethyl acetate. The mixture is separated, and the organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-carboxymethoxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.83 g). MS (m/z): 695 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-carboxymethoxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (200 mg) is dissolved in tetrahydrofuran (4 ml), and thereto are added ethyl aminoacetate hydrochloride (48 mg), 1-hydroxybenzotriazole dihydrate (47 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (66 mg), and triethylamine (49 µl), and the mixture is stirred at room temperature for one hour. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{5-[(ethoxycarbonylmethylcarbamoyl)methoxy]pyrimidin-2-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (165 mg). MS (m/z): 780 $[M+H]^+$

Examples 188-190

The corresponding starting compounds are treated in a similar manner to Example 187 (3) to give the compounds as listed in Table 27.

washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[5-(2-benzyloxycarbonylaminoethoxy)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (249 mg). MS (m/z): 814 $[M+H]^+$

(2) (2R,4S)-4-{[5-(2-Benzyloxycarbonylaminoethoxy)pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (240 mg) is dissolved in methanol (5 ml), and thereto is added 10 % palladium-carbon (100 mg), and the mixture is stirred under hydrogen atmosphere for 2 hours. The reaction solution is filtered and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 7:3→2:3) to give (2R,4S)-4-{[5-(2-aminoethoxy)-pyrimidin-2-yl]-[3,5-bis(trifluoromethyl)benzyl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (167 mg). MS (m/z): 680 $[M+H]^+$

Example 214

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (975 mg) is dissolved in N,N-dimethylformamide (4.5 ml), and thereto is added sodium hydride (62.7 %, 70 mg) under ice-cooling, and the mixture is stirred for 10 minutes. To the reaction solution is added 4-bromobutyronitrile (0.2 ml), and the mixture is stirred at room temperature for one hour. To the reaction solution are added water and ethyl acetate under ice-cooling, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)pyrimidin-2-

yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.1 g). MS (m/z): 704 $[M+H]^+$

Example 215

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg), sodium azide (462 mg), and ammonium chloride (380 mg) are dissolved in N,N-dimethylformamide (1 ml), and the mixture is stirred at 120°C for 27 hours. The reaction solution is cooled to room temperature, and thereto are added 1N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{5-[3-(tetrazol-5-yl)propoxy]pyrimidin-2-yl}}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (169 mg). MS (m/z): 747 $[M+H]^+$

Example 216

(2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(3-cyanopropoxy)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (700 mg), hydroxylamine hydrochloride (140 mg) and sodium carbonate (212 mg) are dissolved in ethanol (3 ml), and the mixture is refluxed for 41 hours. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-{5-[3-(N-hydroxycarbamimidoyl)propoxy]pyrimidin-2-yl}}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (502 mg). MS (m/z): 737 $[M+H]^+$

are removed by filtration, and the filtrate is concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→7:3) to give (2R,4S)-4-{[3,5-bis-(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfanyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (705 mg). MS (m/z): 725 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfanyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (500 mg) is dissolved in chloroform (2 ml), and thereto is added m-chloroperbenzoic acid (75 %, 636 mg) under ice-cooling. The mixture is stirred at room temperature for one hour, and thereto are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by NH-silica gel column chromatography (hexane:ethyl acetate = 7:3→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfonyl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (309 mg). MS (m/z): 757 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-hydroxybutylsulfonyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (300 mg) and 1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (269 mg) are dissolved in methylene chloride (2 ml), and the mixture is stirred for 2.5 hours. Water and ethyl acetate are added to the mixture, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(3-carboxypropylsulfonyl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-

$[M+H]^+$

(6) (2R,4S)-4-(5-Bromopyrimidin-2-yl)amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.0 g) is dissolved in N,N-dimethylformamide (15 ml), and thereto is added sodium hydride (177 mg) under ice-cooling. The mixture is stirred at the same temperature for 20 minutes, and thereto is added 3,5-bis(trifluoromethyl)benzyl bromide (1.03 ml), and the mixture is stirred at the same temperature for one hour. To the reaction solution are added ethyl acetate and water, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→3:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.19 g). MS (m/z): 761/763 $[M+H]^+$

(7) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.15 g), isonipecotic acid ethyl ester (634 µl), sodium tert-butoxide (407 mg) and 2-(di-tert-butylphosphino)biphenyl (337 mg) are dissolved in toluene (20 ml), and thereto is added tris(dibenzylideneacetone)dipalladium (258 mg), and the mixture is stirred at room temperature under nitrogen atmosphere overnight. To the reaction solution are added ethyl acetate and water, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.30 g). MS (m/z): 838 $[M+H]$

(8) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (1.28 g) is dissolved in ethanol (15 ml), and thereto is added 10 % palladium-carbon (200 mg), and the mixture is stirred at room temperature under hydrogen atmosphere for 1.5 hour. The palladium-carbon is removed by filtration, and the obtained filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonylpiperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1.02 g). MS (m/z): 704 $[M+H]^+$

(9) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonyl-piperidin-1-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (250 mg) and triethylamine (60 µl) are dissolved in methylene chloride (3 ml), and thereto is added triphosgene (42 mg) under ice-cooling. The mixture is stirred at room temperature for 30 minutes, and thereto are added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in tetrahydrofuran (1 ml), and thereto are added a 2-fluoroethanol (0.5 ml), triethylamine (0.5 ml) and 4-dimethylaminopyridine (10 mg), and the mixture is stirred at room temperature overnight. To the mixture are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (hexane:ethyl acetate = 95:5→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(4-ethoxycarbonylpiperidin-1-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-fluoroethyl ester (215 g). MS (m/z): 794 $[M+H]^+$

yl)}amino-2-ethyl-6-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (13.7 g) is dissolved in methylene chloride (100 ml), and the mixture is cooled to -70°C, and thereto is added dropwise boron tribromide (1M methylene chloride solution, 41.4 ml) under nitrogen atmosphere. The reaction solution is gradually warmed to room temperature with stirring over a period of 1.5 hour. The mixture is further stirred at room temperature for 21 hours. To the reaction solution are added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 19:1→1:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.1 g). MS (m/z): 647/649 $[M+H]^+$

(2) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.1 g), imidazole (0.98 g), and tert-butyldimethylsilyl chloride are dissolved in N,N-dimethylformamide (25 ml), and the mixture is stirred at room temperature for 15.5 hours. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R*,4S*)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-6-(tert-butyldimethylsilanyloxy)-2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.88 g). MS (m/z): 761/763 $[M+H]^+$

(3) (2R*,4S*)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-6-(tert-butyldimethylsilanyloxy)-2-ethyl-3,4-dihydro-2H-

yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1.79 g). MS (m/z): 626/628 [M+H]+

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline (800 mg) is dissolved in dichloromethane (6 ml), and thereto is added triethylamine (444 µl) and triphosgene (303 mg), and the mixture is stirred at room temperature for 5 hours. The reaction solution is concentrated under reduced pressure, and the insoluble materials are removed by filtration with diethyl ether. The filtrate is concentrated under reduced pressure, and the resulting residue is dissolved in tetrahydrofuran (6 ml), and to the mixture are added a 60 % sodium hydride (92 mg) and 1,5-pentanediol (400 mg) under ice-cooling. The mixture is stirrd at room temperature for 30 minutes, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a 1N hydrochloric acid, water, and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-hydroxypentyl ester (643.6 mg). MS (m/z): 757/759 [M+H]+

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-hydroxypentyl ester (640 mg) is dissolved in acetone (5 ml), and thereto is added a 1.94M Jones reagent (1.38 ml) under ice-cooling, and the mixture is stirred for 1.5 hour. To the reaction solution are added sodium hydrogenesulfite and water under ice-cooling, and the mixture is concentrated under reduced pressure. To the resulting residue is added 1N hydrochloric acid and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The

resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester (517.2 mg). MS (m/z): 771/773 $[M+H]^+$

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-carboxybutyl ester (510 mg) is dissolved in tetrahydrofuran: methanol (5:1, 6 ml), and thereto is added a 2M solution of trimethylsilyldiazomethane in hexane (0.86 ml) under ice-cooling, and the mixture is stirred for one hour and 40 minutes. The reaction solution is concentrated under reduced pressure, and the resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (466 mg). MS (m/z): 785/787 $[M+H]^+$

(5) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (460 mg) is dissolved in toluene (3.5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (54 mg), 2-(di-tert-butylphosphino)biphenyl (36 mg), sodium tert-butoxide (112 mg) and morpholine (102 µl), and the mixture is stirred at room temperature for 3 hours. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated aqueous citric acid solution, water, and a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (chloroform:methanol = 1:0→9:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-

$[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (500 mg) is dissolved in dichloromethane (4 ml), and thereto are added triethylamine (556 µl) and triphosgene (380 mg), and the mixture is stirred at room temperature for 1.5 hour. The reaction solution is concentrated under reduced pressure, and thereto is added diethyl ether, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and the resulting residue is dissolved in tetrahydrofuran (4 ml), and thereto are added 6-hydroxyhexanonic acid ethyl ester (156 µl) and triethylamine (167 µl), and the mixture is stirred at room temperature for 30 minutes. To the mixture is added a 60 % sodium hydride (38 mg) under ice-cooling, and the mixture is stirred for 30 minutes. To the reaction solution are added water and ethyl acetate, and the mixture is separated. The organic layer is washed with a 1N hydrochloric acid, water, and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→4:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline -1-carboxylic acid 5-ethoxycarbonylpentyl ester (380 mg). MS (m/z): 813/815 $[M+H]^+$

(3) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (370 mg) is dissolved in toluene (2.5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (42 mg), 2-(di-tert-butylphosphino)biphenyl (27 mg), sodium tert-butoxide (87 mg) and morpholine (79 µl), and the mixture is stirred at room temperature for 30 minutes. The mixture is stirred at 80°C for one hour and 45 minutes. The reaction solution is cooled to room temperature, and thereto are added water and ethyl acetate, and the mixture is separated. The organic layer is

washed with a 1N hydrochloric acid, water, and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 9:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (90.3 mg, MS (m/z): 820 $[M+H]^+$) and (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester (67.7 mg, MS (m/z): 792 $[M+H]^+$).

(4) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)-pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-ethoxycarbonylpentyl ester (90 mg) is dissolved in ethanol (1 ml), and thereto is added a 2N aqueous sodium hydroxide solution (0.16 ml), and the mixture is stirred at room temperature for 2 hours. To the reaction solution are added a 1N hydrochloric acid (0.32 ml) and ethyl acetate, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→1:1) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-[5-(morpholin-4-yl)pyrimidin-2-yl]}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 5-carboxypentyl ester (53 mg). MS (m/z): 792 $[M+H]^+$

Example 276

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinoline (1 g) is dissolved in toluene (3.5 ml), and thereto are added tris(dibenzylideneacetone)dipalladium (137 mg), 2-(di-tert-butylphosphino)biphenyl (95 mg), sodium tert-butoxide (460mg) and morpholine (0.28 ml), and the mixture is

to Example 50 to give the compound of Example 293. MS (m/z): 801 $[M+H]^+$

Example 294

(1) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-bromopyrimidin-2-yl)}-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (1.08 g) is dissolved in dimethylsulfoxide (4 ml), and thereto are added [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium, complex with dichloromethane (1:1, 30 mg), potassium acetate (403 mg), and bis(pinacolato)diboron (522 mg), and the mixture is stirred at 80°C for 2 hours. The reaction solution is cooled to room temperature, and thereto are added water and diethyl ether, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in tetrahydrofuran (4 ml), and thereto is added a 30 % aqueous hydrogen peroxide solution (1.0 ml) under ice-cooling, and the mixture is stirred at room temperature for 7.5 hours. To the reaction solution is added a saturated aqueous sodium thiosulfate solution under ice-cooling, and then further added diethyl ether, and the mixture is separated. The organic layer is washed with water and a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by silica gel column chromatography (hexane:ethyl acetate = 4:1→3:2) to give (2R,4S)-4-{[3,5-bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (1.06 mg). MS (m/z): 723 $[M+H]^+$

(2) (2R,4S)-4-{[3,5-Bis(trifluoromethyl)benzyl]-(5-hydroxypyrimidin-2-yl)}amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonylbutyl ester (200 mg) is dissolved in tetrahydrofuran (3 ml), and thereto are added a 40 % solution of diethyl azodicarboxylate in toluene (255 ml), triphenylphosphine (147 mg), and 2-methoxyethanol (44

concentrated under reduced pressure. The residue is dissolved in ethanol (40 ml), and thereto is added dropwise water (17 ml). The precipitated crystals are collected by filtration, and washed with a mixture of ethanol-water = 7:3 to give (2R*,4S*)-2-ethyl-6,7-ethylenedioxy-4-benzyloxycarbonylamino-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5.98 g). MS (m/z): 458 $[M+H_2O]^+$

(4) (2R*,4S*)-4-Benzyloxycarbonylamino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5.97 g) is dissolved in methanol (60 ml), and thereto are added 10 % palladium-carbon (0.5 g) and ammonium formate (2.14 g), and the mixture is stirred at 37°C for one hour. The palladium-carbon is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is dissolved in chloroform (65 ml), and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. To the resulting residue is added heptane (20 ml), and the mixture is stirred overnight. The precipitated crystals are collected by filtration and washed with heptane to give (2R*,4S*)-4-amino-2-ethyl-6,7-ethylenedioxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3.54 g). MS (m/z): 307 $[M+H]^+$

Reference Example 4

To (2R*,4S*)-6-bromo-2-ethyl-4-(benzyloxycarbonylamino)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (28.36 g), which prepared by treating the corresponding starting compounds in a similar manner to Reference Example 3 (1)-(3), is added a 25 % solution of hydrogen bromide in acetic acid (140 ml), and the mixture is stirred at room temperature for 45 minutes. The reaction solution is concentrated under reduced pressure, and to the residue is added ether (200 ml), and the precipitates are collected by filtration and washed with ether. The precipitates are added to a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer

TRATADO DE COOPERACION DE PATENTES

PCT

INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

(Capitulo II del Tratado de Cooperación de Patentes)

(Artículo 36 y Regla 70 del PCT)

Archivo de referencia del solicitante o del agente **665083**	**PARA ACCION POSTERIOR** Ver Forma **PCT/IPEA/416**	
Solicitud internacional No **PCT/JP2005/006894**	Fecha de presentación internacional (día/mes/año) **01.04.2005**	Fecha de prioridad (día/mes/año) **02.04.2004**
Clasificación Internacional de Patente (IPC) o Clasificación Nacional y IPC **INV. C07D491/04 C07D401/14 C07D401/04 A61K31/47 A61K31/4545 A61K31/444 A61K31/4439 A61P3/06**		
Solicitante **TANABE SEIYAKU CO., LTD.**		

1 Este informe de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional de acuerdo con el Artículo 35 y se transmite al solicitante de acuerdo con el Artículo 36

2 Este INFORME consiste en un total de 9 hojas, incluyendo esta carátula

3 Este reporte también está acompañado por ANEXOS que comprenden:

a [X] (Se envía al solicitante y a la Oficina Internacional) un total de 25 hojas, como sigue

[X] hojas de descripción, reivindicaciones y/o dibujos que han sido modificacióndos y son la base de este informe y/o hojas que contienen rectificaciones hechas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas)

[ ] hojas que reemplazarán hojas anteriores, pero que esta Autoridad considera que contiene modificaciones que van más allá de lo revelado en la solicitud internacional tal como fue presentada, como se indica en el numeral 4 del cuadro No. I y del cuadro suplementario

b [ ] (enviados solamente a la Oficina Internacional) un total de (indique el tipo y el número del portador(es) electrónico(s)) _____, contiene la lista de secuencias y/o tablas relacionadas, solamente en formato de lectura en computador, como se indica en el cuadro suplementario relacionado con la lista de secuencias (ver sección 802 de las instrucciones administrativas)

4 Este informe contiene indicaciones relacionadas con los siguientes items.

[X]	Cuadro No I	Base del informe
[ ]	Cuadro No. II	Prioridad
[X]	Cuadro No. III	No establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicación industrial
[X]	Cuadro No. IV	Carencia de unidad de la invención
[X]	Cuadro No. V	Declaración razonada segun articulo 35(2) con relacion a la novedad,nivel inventivo o aplicación industrial; citas y explicaciones que apoyan tal declaración
[ ]	Cuadro No. VI	Ciertos documentos citados
[X]	Cuadro No. VII	Ciertos defectos en la solicitud internacional
[ ]	Cuadro No VIII	Ciertas observaciones sobre la solicitud internacional

Fecha de presentación de la solicitud de examen	Fecha de completamiento de este informe
01.02.2006	**10.07.2006**
Nombre y dirección de correo del IPEA: Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario autorizado **Schmid, A** Telephone No. +49 89 2399-8591

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No
PCT/JP2005/006894

Cuadro No. I Base del Informe

1 Con relación al idioma, este reporte se basa en

[X] La solicitud internacional en el idioma como fue presentada

[ ] La traducción dentro de la solicitud internacional, con el idioma de la traducción suministrada para dicho propósito.

[ ] búsqueda internacional (bajo las Reglas 12.3(a) y 23 1(b)).

[ ] publicación de la solicitud internacional (bajo la Regla 12.4(a))

[ ] examen preliminar internacional (bajo las Reglas 55 2 y/o 55.3(a))

2 Con relación a los elementos de la solicitud Internacional dicho reporte se basa en (Las hojas de reemplazo que se han suministrado a la Oficina de Recepción en respuesta a una invitación según el articulo 14, se denominan en este informe como "presentadas originalmente" y no se anexan a este informe).

Descripción, páginas

1-87, 89-93, 95-104, 106-126, 128-147, 149, 152, 153, 156-164, 167, 169-171, 173-181, 184-188, 190-214, 217-229, 231-235, 238, 239, 242-254, 256-261, 263-265 — como se presentaron originalmente

88, 94, 105, 127, 148, 150, 151, 154, 155, 165, 166, 168, 172, 182, 183, 189, 215, 216, 230, 236, 237, 240, 241, 255, 262 — recibidas en 01.02 2006 con carta de 30 01.2006

Reivindicaciones, Números

1 - 26 como se presentaron originalmente

[ ] la lista de secuencia y/o cualquiera relacionada con la(s) tabla(s) - ver Cuadro Suplementario Relacionado con la Lista de la Secuencias

3 [ ] Las modificaciones han dado como resultado la cancelación de:

- [ ] la descripción, páginas _____
- [ ] las reivindicaciones, Nos. _____
- [ ] los dibujos, hojas/fig. _____
- [ ] la lista de secuencias _____
- [ ] cualquier tabla(s) relacionada con la lista de secuencias _____

4 [ ] Este informe ha sido establecido como si (parte de) las modificaciones no han sido hechas,ya que se consideran que han ido más allá de lo revelado que fue presentado, como se indica en la casilla suplementar a (Regla 70 2 (c)).

- [ ] la descripción, paginas _____.
- [ ] las reivindicaciones, Nos. _____
- [ ] los dibujos, hojas/fig. _____
- [ ] la lista de secuencias _____
- [ ] cualquier tabla(s) relacionada con la lista de secuencias _____

* Si el numeral 4 aplica, algunas o todas las páginas pueden marcarse como "reemplazadas".

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/JP2005/006894

Cuadro No. III No establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicación industrial

1 El cuestionamiento de si la invención reclamada parece ser novedosa, tiene nivel inventivo (no es obvia), o tiene aplicación industrial, no se ha examinado para·

[ ] La solicitud internacional completa

[X] Reivindicaciones Nos 25, 26

porque.

[X] Dicha solicitud internacional o dichas reivindicaciones 25, 26 se relacionan con el siguiente tema que no requiere de un examen preliminar internacional (especifico)

ver hoja separada

...

Cuadro No. IV Carencia de unidad de la invención

..

2 [X] Dicha autoridad encontró que el requerimiento de unidad de invención no se cumplió y se escogió de conformidad con la regla 68.1, no solicitar al solicitante limitar o pagar tasas adicionales.

3 Dicha autoridad considera que el requerimiento de la unidad de invención de acuerdo con las Reglas 13 1, 13 2 y 13.3, es

..

[X] No se cumplió por las siguientes razones:

ver hoja separada

4 Consequentemente las siguientes partes de la solicitud internacional fueron el tema del examen preliminar internacional, en establecer este informe:

[X] Todas las partes

Cuadro No.V Declaración razonada según articulo 35(2) con relación a la novedad,nivel inventivo o aplicación industrial; citas y explicaciones que apoyan tal declaración

1 Declaración

Novedad (N)	Reivindicaciones	1-26	Si
	Reivindicaciones		No
nivel inventivo (IS)	Reivindicaciones	1-19, 21-26	Si
	Reivindicaciones	20	No
Apliccion industrial (IA)	Reivindicaciones	1-24	Si
	Reivindicaciones		No

2 Citas y explicaciones (Regla 70.7)

ver hoja separada

Cuadro No. VII Ciertos defectos en la solicitud internacional

Los siguientes defectos en la forma o contenido de la solicitud internacional han sido notados

ver hoja separada

Re Ítem III

No se establece opinión con respecto a la novedad, el nivel inventivo y la aplicación industrial.

1) Esta autoridad considera que las reivindicaciones 25 y 26 se relacionan con un tema cubierto por las disposiciones de la regla 67.1 (iv) del PCT. En consecuencia, no se dará opinión acerca de la aplicación industrial del contenido de estas reivindicaciones (Artículo 34 (4) (a) (I) PCT).

Re Ítem IV
Falta de unidad de invención

1) El examinador está de acuerdo con el razonamiento establecido en el informe de búsqueda.

Re Item V
Afirmacion razonada con relación a la novedad, el nivel inventivo o la aplicación industrial; citaciones y explicaciones que apoyan tal afirmación

1) Se hace referencia a los siguientes documentos:

D1: WO 00/17165 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MAGNUS-ARYITEY, GEORGE, T) MARZO 30 2000 (2000-03-30)
D2: WO 00]/17166 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MULARSKI, CHRISTIAN, JAME) Marzo 30 2000 (2000-03-30)
D3: FR-A-2 763 590 (SYNTHELABO) Noviembre 27 de 1998 (1998-11-27)
D4: WO 98/38194 A (RHONE-POULENC RORER S.A; HARDY, JEAN-CLAUDE; BOUQUEREL, JEAN; NEMECEK) Septiembre 3 1998 (1998-09-03)
D5: WANG C ET AL: "Diseño de una alta afinidad del agonista opioide peptidomimetico de los modelos farmacóforo péptido" BIORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol.8, no. 19, Octubre 6 de 1998 (1998-10-06) páginas 2585-2688, XP004139601 ISSN: 0960-894X
D6: M.E.HICKS ET AL: "Efecto diferencial del nuevo opioide no-peptídico 4-tirosilamido-6-benzil-1,2,3,4 tetrahidroquinolina (CGPM-9) in vitro en una rata de funciones t linfocito y macrofago" LIFE SCIENCE, vol, 68, no.24, 2001, páginas 2685-2694, XP002354487

Invención 1:

1) La materia reclamada en las actuales reivindicaciones 1-19, y 24-26 difieren del arte anterior representados por D1 y D2 esencialmente en los sustituyentes presentes de R5 (grupo heterocíclico) lo que no es posible en D1 y D2.

En consecuencia, la materia de las reivindicaciones 1-19 y 24-26 es nueva de acuerdo al artículo 33 (2) PCT.

2) Una persona experta en el arte en búsqueda de compuestos alternativos útiles en la inhibición de CETP seguramente no trataría de modificar los compuestos conocidos justamente en la forma como se reivindicó en la presente solicitud con una expectación razonable de éxito para obtener compuestos con una actividad deseada como pudo probarse por el solicitante en la tabla de la pagina 90.

Por lo tanto, el contenido de la invención de la reivindicación 1 también involucra nivel inventivo con respecto al Artículo 33 (3) del PCT.

3) Para la evaluación de las presentes reivindicaciones 25 y 26 en cuanto si éstas tienen aplicación industrial, no existe un criterio unificado en los estados contratantes del PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. Por ejemplo, la Oficina de Patentes Europea, no reconoce aplicación industrial al contenido de las reivindicaciones que utilizan un compuesto en un tratamiento médico, pero pueden permitir, sin embargo, reivindicaciones de primer uso de compuestos conocidos en el tratamiento médico y el uso de tal compuesto en la elaboración de un medicamento para un nuevo tratamiento médico.

Invención 2:

1) Los documentos D3 a D6 (cf especificaciones en el informe de búsqueda) revelan compuestos que están dentro de la formula general XIII-a ya que el presente grupo R_{15} cubre todos los grupos tal como se revelaron en D3 a D6.

Sin embargo, ya que los documentos D3 a D6 no revelan específicamente un grupo de protección óptimamente activa, el contenido de la presente reivindicación 20 es novedosa de acuerdo con el Artículo 33(2) del PCT.

La patentabilidad de las presentes reivindicaciones 21 a 23 depende de la reivindicación 20. Por lo tanto, se considera que posee novedad el contenido de las presentes reivindicaciones 21 a 23.

2) Aunque el contenido de la presente reivindicación 20 puede considerarse como formalmente novedoso, es bastante claro para una persona experta en síntesis química el uso de un grupo óptimamente activo, si se requiere un producto terminado óptimamente activo (que es el propósito de los compuestos XIII-a).

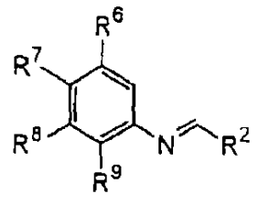
En consecuencia, el contenido de la presente reivindicación 20 no es inventivo y por lo tanto, no cumple con los requerimientos del Artículo 33 (3) del PCT

3) Las presentes reivindicaciones 21 a 23 tienen que ver con métodos cuyo principio general no se conoce del estado de la técnica y no puede derivarse de éstos.

Por lo tanto, el contenido de las presentes reivindicaciones 21 a 23 involucran un nivel inventivo de acuerdo con el Artículo 33 (3) del PCT.

Re Ítem VII
Algunos defectos en la solicitud internacional
1) D3-D6 que representan documentos muy relevantes deberían referirse en la descripción, de acuerdo con la regla 5 (1) (a) (ii) del PCT.

Un compuesto de la fórmula (XIII) también puede ser preparado haciendo reaccionar un compuesto de la fórmula (XIV) con un compuesto de la fórmula (XVIII).



(XVIII)

Esta reacción puede ser realizada de la misma manera como la reacción de un compuesto de la fórmula (XIV) con un compuesto de la fórmula (XV).

Adicionalmente, los sustituyentes respectivos R^1, R^5, R^6, R^7, R^8 y R^9 pueden ser convertidos en un sustituyente conveniente de acuerdo con cualquiera de los procedimientos del PROCEDIMIENTO 4-(A) a (K) y de (1) a (58).

Un compuesto de la fórmula (IV) puede ser preparado por condensación de un compuesto de la fórmula (X) con un compuesto de la fórmula (III)

$$R^{10}\text{-}R^4\text{-}Z^1 \qquad \text{(III)}$$

en donde los símbolos tienen el mismo significado como el definido anteriormente.

La condensación puede ser realizada de la misma manera como se describe precedentemente en WO00/17165 o PROCEDIMIENTO 1.

Un compuesto de fórmula (IX) puede ser preparado por condensación de un compuesto de la fórmula (IV) con un

Ejemplo 9

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (600 mg) y 2-cloro-5-propilpirimidina (1,5 g) fueron disueltos en 1,3-dimetilimidazolidinona (10 ml), y la mezcla fue agitada a 135°C durante 72 horas. La solución de reacción fue enfriada la temperatura ambiente, y fueron agregados a los mismos el agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 6:1→4:1) para dar etil éster de ácido (2R,4S)-2-etil-4-(5-propilpirimidin-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (250 mg). MS (m/z): 437 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-2-etil-4-(5-propilpirimidin-2-il)amino-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (240 mg) y bromuro de 3,5-bis(trifluorometil)bencilo (337 mg) fueron disueltos en N,N-dimetilformamida (3 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 32 mg) a la temperatura ambiente, y la mezcla fue agitada a la misma temperatura durante 2 horas. Fue agregado a la solución de reacción el ácido acético, y fueron agregados agua y acetato de etilo a los mismos. La capa orgánica fue secada sobre sulfato del magnesio, y fue

para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-nitropiridin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (650 mg). MS (m/z): 665 $[M+H]^+$

Ejemplo 28

(1) Etil éster de ácido (2R,4S)-4-[3,5-Bis(trifluorometil)bencil]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (600 mg) fue disuelto en etanol (5,0 ml), y fueron agregados a los mismos bromuro de cianógeno (129 mg) y carbonato de hidrógeno de sodio (283 mg), y la mezcla fue agitada a la temperatura ambiente durante 23 horas y 15 minutos. Fue agregada agua destilada a la mezcla, y la mezcla se extrajo con éter. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-ciano}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (581 mg). MS (m/z): 585 $[M+H_2O]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-ciano)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (50 mg) fue disuelto en N,N-dimetilformamida (1 ml), y fueron agregados a los mismos azida de sodio (57,2 mg) y cloruro de

éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-nitrotiazol-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (58 mg). MS (m/z): 671 $[M+H]^+$

Ejemplo 89

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-ciano}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (327,9 mg) fue disuelto en tetrahidrofurano (3 ml), y a los mismos fue agregado hidruro de sodio (62,7%; 13,9 mg). La mezcla fue agitada con enfriamiento con hielo dentro de una atmósfera nitrógeno durante una hora. A la solución de reacción fue agregado en forma lenta una solución de 3-buten-1-ol (41,8 mg) en tetrahidrofurano (4 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a temperatura ambiente durante 29 horas. Fue agregada agua destilada bajo enfriamiento con hielo, y la mezcla fue extraída con acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo 4:1) para dar etil éster de ácido (2R,4S)-4-{1-[3,5-bis(trifluorometil)bencil]-2-(3-buten-1-il)}isoureido-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (186,3 mg). MS (m/z): 640 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{1-[3,5-Bis(trifluorometil)bencil]-2-(3-buten-1-il)}isoureido-2-etil-

(2) Etil éster de ácido (2R,4S)-4-[(terc-butoxicarbonil)-(5-bromopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (5 g) fue disuelto en 1,4-dioxano (60 ml), y fueron agregados a los mismos bencil éster de ácido acrílico (2,83 g), tris(dibencilidenacetona)-dipaladio (1,2 g), tetrafluoroborato de tri(terc-butil)fosforo (760 mg), y N,N diciclohexilmetilamina (1,87 g). La mezcla fue agitada a temperatura ambiente dentro de una atmósfera de nitrógeno durante 2,5 horas, y fue agregada a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio. La mezcla fue extraída con acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-{(terc-butoxicarbonil)-[5(2-benciloxicarbonilvinil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,65 g). MS (m/z): 655 $[M+H]^+$

(3) Etil éster de ácido (2R,4S)-4-{(terc-butoxicarbonil)-[5-(2-benciloxicarbonilvinil)pirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (3,65 g) fue disuelto en cloruro de metileno (10 ml), y a los mismos fueron agregados ácido trifluoracético (1 ml). La mezcla fue

presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-{(3,5-dimetoxibencil)-[5-(3-hidroxipropil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (68 mg). MS (m/z): 603 $[M+H]^+$

Ejemplo 143

Etil éster de ácido (2R,4S)-4-[(3,5-Dimetoxibencil)-(5-iodopirimidin-2-il)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (302 mg) fue disuelto en N,N-dimetilformamida (2,5 ml), y fueron agregados a los mismos tetrakis(trifenilfosfina)paladio (104 mg), ácido pirimidin-5-borónico (112 mg) y carbonato de sodio (114 mg). La mezcla fue agitada a 100°C en una atmósfera de nitrógeno durante 4 horas. La mezcla fue enfriada a temperatura ambiente, y a los mismos fue agregado agua. La mezcla fue extraida con acetato de etilo, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 2:1) para producir etil éster de ácido (2R,4S)-4-[([5,5']bipirimidin-2-il)-(3,5-dimetoxibencil)]amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (106 mg).

MS (m/z):,623 $[M+H]^+$

mg). La mezcla fue agitada a temperatura ambiente dentro de una atmósfera de hidrógeno durante 3 horas. El catalizador (10 % el paladio-carbono) fue separado por filtración, y el filtrado fue concentrado bajo presión reducida, y el residuo resultante fue purificado por cromatografía en columna (gel de NH-sílice; hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(piperazin-1-il)pirimidin-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (470 mg). MS (m/z): 667 $[M+H]^+$

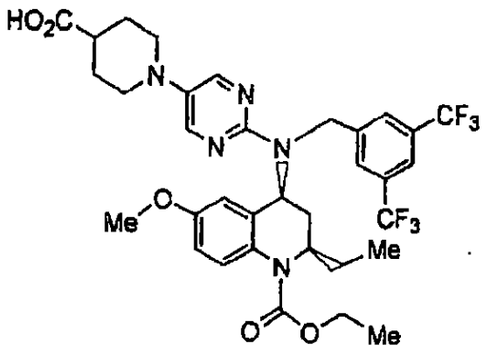
Ejemplo 151

(1) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(piperazin-1-il)pirimidir-2-il]}amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (100 mg) y piridina (18 µl) fueron disueltos en cloruro de metileno (1 ml), y fue agregado a los mismos cloruro de ácido acetoxiacético (19,4 µl) a temperatura ambiente. La mezcla fue agitada toda la noche, y fue lavada con ácido clorhídrico 1N. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna (gel de sílice; hexano:acetato de etilo = 7:3→2:3) para dar etil éster de ácido (2R,4S)-4-({5-[4-(2-acetoxiacetil)piperazin-1-

il)pirimidin-2-il}-[3,5-bis(trifluorometil)bencil])amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (110 mg). MS (m/z): 767 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-({5-[4-(2-acetoxiacetil)piperazin-1-il]pirimidin-2-il}-[3,5-bis(trifluorometil)bencil])amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (87 mg) fue disuelto en etanol (1 ml), y a los mismos fue agregado carbonato de potasio (23 mg) a temperatura ambiente, y la mezcla fue agitada toda una noche. Los materiales insolubles fueron eliminados por filtración, y el filtrado fue concentrado bajo presión reducida para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-{5-[4-(2-hidroxiacetil)piperazin-1-il]pirimidin-2-il})amino-2-etil-6-metoxi-3,4-dihidro-2H-quinolin-1-carboxílico (83 mg). MS (m/z): 725 $[M+H]^+$

Ejemplo 152



Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 124 dar el compuesto del Ejemplo 152. MS (m/z): 710 $[M+H]^+$

purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 6:1→2:1) para dar bencil éster de ácido (2R*,4S*)-4-(5-bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (24,0 g). MS (m/z): 535/537 $[M+H]^+$

(6) Bencil éster de ácido (2R*,4S*)-4-(5-Bromopirimidin-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (13 g) fue tratado de una manera similar a la del Ejemplo 1-(2) para dar bencil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (20,6 g). MS (m/z): 761/763 $[M+H]^+$

(7) Bencil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (18,3 g) fue tratado de una manera similar a la del Ejemplo 1-(3) para dar bencil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-3,4-dihidro-6-trifluorometil-2H-quinolin-1-carboxílico (11,2 g). MS (m/z): 768 $[M+H]^+$

(8) Bencil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)-pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (11,2 g) fue tratado de una manera similar a la del Ejemplo 150 para dar (2R*,4S*)-4-

{[3,5bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (8,9 g). MS (m/z): 634 $[M+H]^+$

Ejemplo 174

(2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina (500 mg) y trietilamina (132 µl) fueron disueltos en cloruro de metileno (5 ml), y a los mismos fueron agregados trifosgeno (94 mg) a temperatura ambiente, y la mezcla fue agitada durante una hora. La solución de reacción fue concentrada bajo presión reducida, y el residuo resultante fue separado dentro de acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (5 ml), y glicol etilénico (0,5 ml), fueron agregados a los mismos trietilamina (295 ml) y 4-dimetilaminopiridina (26 mg). La mezcla fue agitada toda la noche a temperatura ambiente. La solución de reacción fue separada dentro de acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel

de sílice (hexano:acetato de etilo = 3:1→2:3) para dar 2-hidroxietil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (430 mg). MS (m/z): 722 $[M+H]^+$

Ejemplo 175

(1) Etil éster de ácido (2R,4S)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,28 g), etil éster de ácido 2-cloroxazol-4-carboxílico (1,44 g) y diisopropiletilamina (1,42 ml) fueron disueltos en 1,4-dioxano (10 ml), y la mezcla fue agitada toda la noche a 130°C. La solución de reacción fue enfriada a temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→1:1) para dar etil éster de ácido (2R,4S)-4-(4-etoxicarboniloxazol-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,13 g). MS (m/z): 456 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-(4-Etoxicarboniloxazol-2-il)amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,12 g) fue tratado de una manera similar a la

presión reducida. El residuo resultante fue disuelto en el tetrahidrofurano (100 ml), y a los mismos fueron agregados de manera lenta una solución acuosa al 30% de agua oxigenada (70 ml) bajo enfriamiento con hielo. Después de pasada una hora, una solución acuosa saturada de tiosulfato de sodio fue agregada a la mezcla, y el exceso de agua oxigenada fue evaporado. La mezcla fue separada en agua y acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 5:1→3:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (19,22 g). MS (m/z): 637 $[M+H]^+$

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (6,5 g) y etil éster de ácido 4-bromobutílico (2,19 g) fue disuelto en N,N-dimetilformamida (50 ml), y a los mismos fueron agregados carbonato de potasio (1,69 g), y la mezcla fue agitada toda la noche a 45°C. Fueron agregados acetato de etilo y agua a la mezcla, y la capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo

(3) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-carboximetoxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (200 mg) fue disuelto en tetrahidrofurano (4 ml); y fueron agregados a los mismos hidrocloruro de amincacetato de etilo (48 mg), dihidrato de 1-hidroxibenzotriazol (47 mg), hidrocloruro de 1-etil-3-(3-dimetilamino-propil)carbodiimida (66 mg), y trietilamina (49 µl), y la mezcla fue agitada a temperatura ambiente durante una hora. Fueron agregados agua y acetato de etilo a la mezcla, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar etil éster de ácido (2R,4S)-4-([3,5-bis(trifluorometil)bencil]-{5-[(etoxicarbonilmetilcarbamoil)metoxi]pirimidin-2-il})amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (165 mg). MS (m/z): 780 $[M+H]^+$

Ejemplos 188-190

Los compuestos de comienzo correspondientes fueron tratados de una manera similar a la del Ejemplo 187 (3) para dar los compuestos enumerados en la Tabla 27.

bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (240 mg) fue disuelto en metanol (5 ml), y fueron agregados a los mismos 10% paladio-carbono (100 mg), y la mezcla fue agitada bajo atmósfera de hidrógeno durante 2 horas. La solución de reacción fue filtrada y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 7:3→2:3) para dar etil éster de ácido (2R,4S)-4-{[5-(2-aminoetoxi)pirimidin-2-il]-[3,5-bis(trifluorometil)bencil]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (167 mg). MS (m/z): 680 $[M+H]^+$

Ejemplo 214

Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (975 mg) fue disuelto en N,N-dimetilformamida (4,5 ml), y fueron agregados a los mismos hidruro de sodio (62,7%; 70 mg) bajo enfriamiento con hielo, y la mezcla fue agitada durante 10 minutos. Fue agregado a la solución de reacción4-bromobutironitrilo (0,2 ml), y la mezcla fue agitada a la temperatura ambiente durante una hora. A la solución de reacción se agregan agua y acetato de etilo bajo enfriamiento con hielo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre

disuelto en N,N-dimetilformamida (25 ml), y la mezcla fue agitada a la temperatura ambiente durante 15,5 horas. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 9:1→4:1) para dar etil éster de ácido (2R*,4S*)-4-{[3,5-bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-6-(terc-butildimetilsilaniloxi)2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (3,88 g). MS (m/z): 761/763 $[M+H]^+$

(3) Etil éster de ácido (2R*,4S*)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-6-(terc-butildimetilsilaniloxi)-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (3,85 g), [1,1'-bis(difenil-fosfino)ferroceno]-dicloropaladio (111 mg), acetato de potasio (1,5 g) y bis(pinacolato)diboro (1,9 g) fueron disueltos en dimetil sulfóxido desaereado (50 ml), y la mezcla fue agitada a 80°C durante 30 minutos. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue

(2) Etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-hidroxibutilsulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (500 mg) fue disuelto en cloroformo (2 ml), y fueron agregados a los mismos el ácido m-cloroperbenzoico (75%, 636 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante una hora, y fueron agregados a los mismos una solución acuosa saturada de carbonato hidrógeno de sodio y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de NH-sílice (hexano:acetato de etilo = 7:3→1:1) para dar etil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-hidroxibutilsulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolinl-carboxílico (309 mg). MS (m/z): 757 $[M+H]^+$

(3) etil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-hidroxibutilsulfonil)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (300 mg) y 1,1,1-tris(acetoxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona (269 mg) fue disuelto en cloruro de metileno (2 ml), y la

etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (2,15 g), etil éster de ácido isonipecótico (634 µl), terc-butóxido de sodio (407 mg) y 2-(di-terc-butilfosfino)bifenilo (337 mg) fue disuelto en tolueno (20 ml), y fueron agregados a los mismos tris(dibencilidenacetona)dipaladio (258 mg), y la mezcla fue agitada toda la noche a la temperatura ambiente bajo atmósfera de nitrógeno. Fue agregado a la solución de reacción acetato de etilo y agua, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→4:1) para dar bencil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,30 g). MS (m/z): 838 $[M+H]^+$

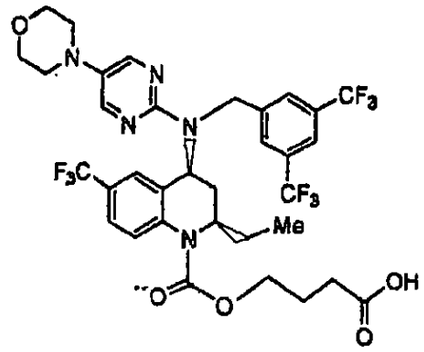
(8) Bencil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,28 g) fue disuelto en etanol (15 ml), y fueron agregados a los mismos 10% paladio carbono (200 mg), y la mezcla fue agitada a la temperatura ambiente bajo atmósfera de hidrógeno durante 1,5 hora. El paladio-carbono

fue eliminado por filtración, y el filtrado obtenido fue concentrado bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→4:1) para dar (2R, 4S)-4-([3,5-bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidro-quinolina (1,02 g). MS (m/z): 704 $[M+H]^+$

(9) (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-[5-(4-etoxicarbonilpiperidin-1-il)pirimidin-2-il]}amino-2-etil-6-trifluorometil-1,2,3,4-tetrahidroquinolina (250 mg) y trietilamina (60 µl) fue disuelto en cloruro de metileno (3 ml), y fueron agregados a los mismos trifosgeno (42 mg) bajo enfriamiento con hielo. La mezcla fue agitada a la temperatura ambiente durante 30 minutos, y fueron agregados a los mismos acetato de etilo y una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo fue disuelto en tetrahidrofurano (1 ml), y fueron agregados a los mismos un 2-fluoroetanol (0,5 ml), trietilamina (0,5 ml) y 4-dimetilaminopiridina (10 mg), y la mezcla fue agitada toda la noche a la temperatura ambiente. A la mezcla se agregan agua y acetato de etilo, y la mezcla fue separada. La capa

agitada a la temperatura ambiente por 3 horas. Fue agregado a la solución de reacciónagua y acetato de etilo, y la mezcla fue separada. La capa orgánica fue lavada con una solución acuosa saturada de ácido cítrico, agua, y una solución salina saturada, fue secada sobre sulfato de sodio, y fue concentrada bajo presión reducida. El residuo resultante fue purificado por la cromatografía en columna de gel de sílice (cloroformo:metanol = 1:0→9:1) para dar 4-carboxibutil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-[5-(morfolin-4-il)pirimidin-2-il]}amino-2-etil-6-trifluorcmetil-3,4-dihidro-2H-quinolin-1-carboxílico (72,5 mg). MS (m/z): 778 $[M+H]^+$

Ejemplo 273



Los compuestos de comienzo correspondientes fueron tratados de manera similar al Ejemplo 272 para dar el compuesto del Ejemplo 273. MS (m/z): 764 $M+H]^+$

Ejemplo 274

(1) 6-metoxicarbonilhexil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-bromopirimidin-2-il)}amino-2-

diclorometano (1:1, 30 mg), acetato de potasio (403 mg), y bis(pinacolato)diboro (522 mg), y la mezcla fue agitada a 80°C durante 2 horas. La solución de reacción fue enfriada a la temperatura ambiente, y fueron agregados a los mismos agua y dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue disuelto en tetrahidrofurano (4 ml), y fueron agregados a los mismos una solución acuosa 30% de agua oxigenada (1,0 ml) bajo enfriamiento con hielo, y la mezcla fue agitada a la temperatura ambiente durante 7,5 horas. Fue agregada a la solución de reacción una solución de tiosulfato de sodio acuosa saturada bajo enfriamiento con hielo, y entonces además fue agregado dietil éter, y la mezcla fue separada. La capa orgánica fue lavada con agua y una solución salina saturada, fue secada sobre sulfato de magnesio y fue concentrada bajo presión reducida. El residuo resultante fue purificado por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 4:1→3:2) para dar 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (1,06 mg). MS (m/z): 723 $[M+H]^+$

(2) 4-metoxicarbonilbutil éster de ácido (2R,4S)-4-{[3,5-Bis(trifluorometil)bencil]-(5-hidroxipirimidin-2-il)}amino-2-

A etil éster de ácido (2R*,4S*)-6-bromo-2-etil-4-(benciloxicarbonilamino)-3,4-dihidro-2H-quinolin-1-carboxílico (28,36 g) que fue preparado tratando los compuestos de comienzo correspondientes de una manera similar al Ejemplo de referencia 3 (1)-(3), fueron agregados una solución 25% de bromuro hidrógeno en ácido acético (140 ml), y la mezcla fue agitada a la temperatura ambiente durante 45 minutos. La solución de reacción fue concentrada bajo presión reducida, y fue agregado al residuo éter (200 ml), y el precipitado fue recolectado por filtración y lavado con éter. El precipitado fue agregado a una solución acuosa saturada de carbonato hidrógeno de sodio, y la mezcla fue extractada con acetato de etilo. La capa orgánica fue lavada con una solución salina saturada, fue secada sobre sulfato de sodio y fue concentrada bajo presión reducida. El residuo fue purificado por cromatografía en columna de gel de sílice (acetato de etilo) y fue concentrada. Al residuo fue agregado heptano (150 ml), y la mezcla fue agitada toda la noche a la temperatura ambiente. El precipitado fue recolectado por filtración y lavado con heptano para dar etil éster de ácido (2R*,4S*)-4-amino-6-bromo-2-etil-3,4-dihidro-2H-quinolin-1-carboxílico (18,46 g). MS (m/z): 327/329 $[M+H]^+$.

Ejemplo de referencia 5

(1) El bromopiruvato de etilo (29,9 g) y urea (13,8 g) fueron disueltos en etanol (110 ml) y la mezcla permaneció a reflujo

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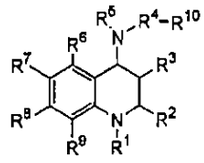
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(85) Fecha límite inicio fase nacional. 02/11/06 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: **01/04/2005** N° de solicitud **PCT/JP2005/006894**	(87) Publicación internacional Fecha: **13/10/2005** N° publicación **WO 2005/095409 A2**

(54) Título: **DERIVADOS DE TETRAHIDROQUINOLINA Y UN PROCEDIMIENTO PARA PREPARAR LOS MISMOS**

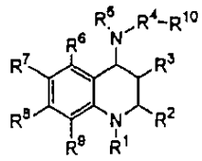
Reivindicación(es)

(19) Un compuesto caracterizado por que posee la fórmula (1):



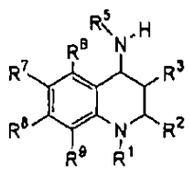
(I)

en donde R^1 es un átomo de hidrógeno, un grupo alcoxicarbonilo opcionalmente sustituido, un grupo carbamoilo opcionalmente sustituido, un grupo alquilo opcionalmente sustituido, un grupo alcanoilo opcionalmente sustituido, un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de oxigeno, azufre y átomos de nitrógeno (el grupo heterocíclico es opcionalmente sustituido), o un grupo carbonilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno (el grupo heterocíclico opcionalmente sustituido),;
R^2 es un átomo de hidrógeno o un grupo alquilo opcionalmente sustituido;
R^3 es un atomo de hidrógeno o un grupo alquilo opcionalmente sustituido,
R^4 es un grupo alquileno opcionalmente sustituido,
(20) R^5 es un grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno, en donde el grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de los grupos siguientes, o dicho grupo heterocíclico es sustituido por 1 a 5 sustituyentes seleccionados de grupos siguientes y además por un átomo halógeno, un grupo oxo y/o hidroxilo:
grupo ciano, grupo nitro, grupo carboxilo, grupo sulfo, grupo alquilo C_{3-10}, grupo alquilo sustituido, grupo cicloalquilo opcionalmente sustituido, grupo alquenilo opcionalmente sustituido, grupo alcoxilo C_{3-10}, grupo alcoxilo sustituido, grupo cicloalcoxilo opcionalmente sustituido, grupo alcoxicarbonilo opcionalmente sustituido, grupo carbamoilo opcionalmente sustituido, grupo carbamimidoilo opcionalmente sustituido, grupo alquiltio opcionalmente sustituido, grupo alquilsulfinilo opcionalmente sustituido, grupo alquilsulfonilo opcionalmente sustituido, grupo amino opcionalmente sustituido, grupo sulfamoilo opcionalmente sustituido, grupo alcanoilo opcionalmente sustituido, grupo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno (el grupo heterocíclico es opcionalmente sustituido), un grupo oxilo monocíclico o heterocíclico bicíclico saturados o no saturado que contiene 1 a 4 heteroátomos seleccionados independientemente de átomos de oxígeno, azufre y nitrógeno (el grupo oxilo heterocíclico es opcionalmente sustituido), y un grupo carbonilo monocíclico o heterocíclico bicíclico saturado o no saturado que contiene 1 a 4 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno (el grupo carbonilo heterocíclico es opcionalmente sustituido),
R^6, R^7, R^8 y R^9 son independientemente un átomo de hidrógeno, un átomo halógeno, un grupo hidroxilo, un grupo nitro, un grupo ciano, un grupo alquilo opcionalmente sustituido, un grupo alcoxilo opcionalmente sustituido, un grupo alquilsulfoniloxilo opcionalmente sustituido o un grupo amino opcionalmente sustituido; o
R^6 y R^7, ó R^7 y R^8, ó R^8 y R^9 pueden combinarse en los extremos para formar un grupo alquileno cuyo grupo alquileno puede contener 1 a 3 heteroatomos independientemente seleccionados de los átomos de nitrógeno, azufre y oxigeno, y puede tener un sustituyente(s); y
R^{10} es un anillo aromático que contiene opcionalmente 1 a 3 heteroátomos independientemente seleccionados de átomos de oxigeno, azufre y nitrógeno (el anillo aromático es opcionalmente sustituido), o una sal farmacéuticamente aceptable del mismo.
Un procedimiento para preparar un derivado tetrahidroquinolina de la fórmula (I):



(I)

en donde los símbolos R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 y R^{10} tienen el mismo significado como el definido en la reivindicación 1, caracterizado por que comprende condensar un compuesto de la formula (II):



(II)

en donde cada simbolo tiene el mismo significado como el definido precedentemente con un compuesto de la fórmula (III)

$$R^{10}\text{-}R^{4}\text{-}Z^{1} \qquad \text{(III)}$$

en donde Z^1 es un grupo de partida y los otros símbolos tienen el mismo significando como el definido anteriormente.

6079-FNP(f) **PATENT COOPERATION TREATY** PCT/JP2005/006894

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To

KAWAMIYA, Osamu
AOYAMA & PARTNERS, IMP Building
3-7, Shiromi 1-chome
Chuo-ku, Osaka-shi
Osaka 5400001
JAPON

Date of mailing *(day/month/year)*
06 September 2006 (06.09.2006)

Applicant's or agent's file reference
665083

IMPORTANT NOTIFICATION

International application No
PCT/JP2005/006894

International filing date *(day/month/year)*
01 April 2005 (01.04.2005)

1 The following indications appeared on record concerning

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
MOTOMURA, Daisuke
c/o TANABE SEIYAKU CO., LTD , 2-10, Dosho-machi 3-chome, Chuo-ku,
Osaka-shi, Osaka
5418505
Japan

State of Nationality: JP
State of Residence: JP
Telephone No
Facsimile No
Teleprinter No

2 The International Bureau hereby notifies the applicant that the following change has been recorded concerning

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
MOTOMURA, Daisuke
504, Domiru-Sagamiono 3-1, Sagamiono 8-chome
Sagamihara-shi, Kanagawa 228-0803
Japan

State of Nationality: JP
State of Residence: JP
Telephone No
Facsimile No
Teleprinter No

3 Further observations, if necessary

4 A copy of this notification has been sent to

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No +41 22 338 82 70

Authorized officer
Chevallay-Worley Madeleine

Facsimile No +41 22 338 70 10
Telephone No +41 22 338 88 59

Form PCT/IB/306 (October 2005) 1/CY5EHBX10

864
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TRATADO DE COOPERACION DE PATENTES

PCT/JP2005/006894

De la OFICINA INTERNACIONAL

PCT

NOTIFICACION DEL REGISTRO DE UN CAMBIO.

(PCT regla 92 bis.1 e instrucciones Administrativas, Sección 422)

Para:

KAWAMIYA, Osamu
AOYAMA & PARTNERS
IMP Building
3-7, Shiromi 1-chome
Chuo-ku, Osaka-shi
Osaka 5400001
JAPON

Fecha de correo (día/mes/año)	
6 de Septiembre de 2006 (06.09.2006)	
Referencia del solicitante o del agente	**NOTIFICACION IMPORTANTE**
665083	
Número de la solicitud internacional	**Fecha de presentación internacional (día/mes/año)**
PCT/JP2005/006894	1 de Abril de 2005 (01 04.2005)

1. La indicación siguiente apareció en el registro concerniente a:

[X] El solicitante [X] El inventor [ ] El agente [ ] El representante común

Nombre y Dirección	Estado de Nacionalidad	Estado de Residencia
MOTOMURA, Daisuke c/o TANABE SEIYAKU CO., LTD. 2-10, Dosho-machi 3-chome, Chuo-ku Osaka-shi, Osaka 5418505 JAPON	JP	JP
	Número telefónico	
	Número de Fax	
	Número de Teleimpresor	

2. La oficina internacional notifica con este formato al solicitante que el siguiente cambio ha sido registrado en:

[ ] La persona [ ] El nombre [X] La dirección [ ] La nacionalidad [ ] La residencia

Nombre y Dirección	Estado de Nacionalidad	Estado de Residencia
MOTOMURA, Daisuke 504, Domiru-Sagamiono 3-1, Sagamiono 8-chome Sagamihara-shi, Kanagawa 228-0803 JAPON	JP	JP
	Número deTeléfono	
	Número de Fax	
	Número de Teleimpresor	

3. Observaciones adicionales, en caso de ser necesario:

4. Una copia de esta notificación se ha enviado a:

[X] La oficina receptora
[ ] La autoridad de búsqueda internacional
[ ] La autoridad del examen preliminar internacional
[ ] Las concernientes oficinas designadas
[X] Las concernientes oficinas elegidas
[ ] otro

La Oficina Internacional WIPO **34, Chemin des Colombettes** **1211 Geneva 20, SUIZA** Fax No. +41 22 338 82 70	Funcionario Autorizado **Chevallay-Worley Madeleine** Fax No +41 22 338 70 10 Teléfono No. +41 22 338 88 59

Formato PCT/IB/306 (Octubre de 2005)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-111125- -00000-0000
Fec: 2006-11-01 14:40:30 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act 411 PRESENTACION
Folios: 004

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRÁMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (X) MODELO DE UTILIDAD ( )	(X)	( )
- Indicación de que se solicita la concesión de una patente	(X)	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	(X)	( )
- Descripción de la invención	(X)	( )
- Dibujos de ser estos pertinentes	( )	( )
- Comprobante de pago de las tasas establecidas	(X)	( )

COMPLETA ( ) INCOMPLETA (X)

DISEÑO INDUSTRIAL ( )

- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

EZQUEMA DE TRAZADO ( )

- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica del Esquema de Trazado	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

Firma responsable. _____

Fecha. _____

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CASTELLANOS ABONDANO MARGARITA
Apoderado(a) y/o Representante de
TANABE SEIYAKU CO., LTD.

REFERENCIA	Radicación No.	6 111125
	Solicitud internacional	PCT/JP2005/006894
	Fecha inicio fase nacional	02/11/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	14639

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 22 DIC. 2006
aalvarado