



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21 EXPEDIENTE No. 03-112806

54 TÍTULO "Nuevos compuestos heterocíclicos y uso
farmacéutico de los mismos

51 CLASIFICACIÓN INTERNACIONAL C07D 217/26

71 SOLICITANTE KYTO PHARMACEUTICAL INNOVATIONS LTD.

DOMICILIO 30, Nishinohyo TSUKINOWA-cho, MAKANJO-KU
KYOTO-shi. Kyoto 604-8447, JAPAN

74 APODERADO DR. MARGARITA CASTELLANOS ARBORELI

22 BOGOTÁ, D. C., 29-Dic 2003

PETITORIO

Industria y Comercio
SUPERINTENDE



03 112806 00

Radicación : 03112806 00000000 Folio(s) : 201
Fecha (MM/AA): 2003-12-29 13:59:44
Trámite : 011 PCT-PATENTE J/9 FOLIO NÚMERO 411 PRESEMINIO
Dependencia: 2029 DIVISION DE NUEVAS CREACIONES

**FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL**

SOLICITUD DE

①

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

②

SOLICITANTE (71)

Nombre KYOTO PHARMACEUTICAL INDUSTRIES, LTD

Dirección 38, Nishinokyo Tsukinowa-cho, Nakakyo-ku, Kyoto-shi, Kyoto 604-8444, JAPON

Nacionalidad o Domicilio Kyoto - JAPON
Lugar de Constitución JAPONTeléfono _____ Fax _____
E-mail _____

IDENTIFICACIÓN

C C ☐ NIT ☐C E ☐ Otro ☐

Cual _____

Número _____

③

REPRESENTANTE
O APODERADO (74)

Nombre MARGARITA CASTELLANOS A.

Dirección CARRERA 9 No 93-09

Teléfono 610 74 80 Fax 610 07 06
E-mail acastell@impest.net.co

IDENTIFICACIÓN

C C ☒ NIT ☐C E ☐ Otro ☐Número 39779 654 TPA 70 818

④

INVENTOR (ES) (72)

Nombre (VER ANEXO No 1)

Dirección

Nacionalidad o Domicilio (VER ANEXO No. 1)

⑤

PCT (86)

Solicitud Internacional No PCT/JP02/05097Fecha 27/05/02Publicación Internacional No WO 02/096880Fecha 5/12/02

⑥

Título (54)

NUEVOS COMPUESTOS HETEROCICLICOS Y USO FARMACEUTICO DE LOS MISMOSFol. 205

⑦

Clasificación Internacional (51)

C07D 213/26

⑧

Prioridad

SI ☒ NO ☐

(33) País de Origen

JP

(32) Fecha

29/05/2001

(31) Número de Solicitud

181489/2001

⑨

Comprobante de pago No.

03-92 898

Fecha

Diciembre 19, 2003

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

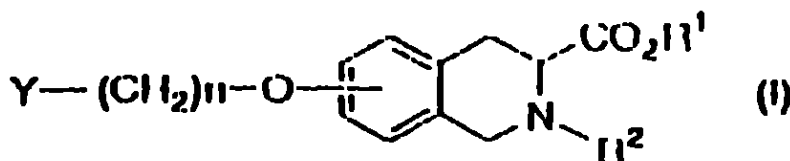
10

Anexos

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
☒ 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
☒ Copia de la solicitud Internacional (Resumen, descripción, reivindicaciones, dibujos)
☒ Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
☐ Copia del examen preliminar Internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
☐ Traducción del examen preliminar Internacional efectuado por la IPEA
☐ De ser el caso, copia del contrato de acceso
☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
☐ De ser el caso, certificado de depósito del material biológico
☒ Arte final 12x12
☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
☐ De ser el caso, modificaciones efectuadas a la solicitud Internacional
☐ Otros

11

FIGURA CARACTERISTICA



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

ALVARO CASTELLANOS M. & CIA.
A B O G A D O S
Carrera 9 No. 83-08
Apartado 8348
Bogotá, D C - COLOMBIA

ANEXO No. 1

INVENTORES

NOMBRE	DOMICILIO	NACIONALIDAD
1 MATSUI, Hiroshi	14-4, Mimatsu 3-chome, Nara-shi, Nara 631-0074 - JAPON	JAPONES
2 KOBAYASHI, Hideo	21-35, Gokashou-Obayashi, Uji-shi, Kyoto 611-0011 - JAPON	JAPONES
3. AZUKIZAWA, Satoru	303, Berumazon-YS, 128-1, Kuze Nakakuze-cho 2-chome, Minami-ku, Kyoto-shi, Kyoto 601 8213 JAPON	JAPONES
4 KASAI, Masayasu	3-1, Seikadai 4-chome, Selka-cho, Souraku-gun, Kyoto 619-0238 -JAPON	JAPONES
5. YOSHIMI, Akihisa	23-1, Jonan-cho 1-chome, Takatsuki-shi, Osaka 569-0056, JAPON	JAPONES
6 SHIRAHASE, Hiroaki	38-35, Imazato Kawahara, Nagaokakyo-shi, Kyoto 617-0814, JAPON	JAPONES

4

Radicación : 83112806 00000000 Folios: 201
Fecha (MM): 2003-12-29 13:59:44
Trámite : 011 PCI-PATENTE A/9 FASE NÚCL 411 MARMINAL
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

CONTABILIZADO Y PAGADO EN

NIT : 000170007-2

RECIBO OFICIAL DE CAJA : 03 - 92.070
FECHA : DICIEMBRE 19 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PASO	BANCO	CUENTA	Nº. PASO	FECHA PASO	VT. PASO
JORGE ELIECER SEPULVEDA	CONSIGNACION	BANCO POPULAR	050-00110-6	4944261	19/12/2003	3.440.000.00

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

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	110 PTC SOLICITUD DE PATENTE DE INVEN	400.000.00
	TOTAL	400.000.00

CON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE Nº. _____

5

ALVARO CASTELLANOS M & CIA
A B O G A D O S
Carrera 9 No. 93-09
Apartado 6349
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 la sociedad KYOTO PHARMACEUTICAL INDUSTRIES, LTD.

Yo, XIMENA CASTELLANOS ABONDANO, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, atentamente manifiesto a Uds que sustituyo en la Dra MARGARITA CASTELLANOS ABONDANO, el poder que me confirió la sociedad KYOTO PHARMACEUTICAL INDUSTRIES, LTD., con domicilio en 38, Nishinokyo Tsukinowa-cho, Nakakyo-ku, Kyoto-shi, Kyoto 604-8444, JAPON, debidamente legalizado por Apostilla bajo el No 04221 el día 4 de Diciembre de 2003, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT entrada en Fase Nacional en Colombia, para "NUEVOS COMPUESTOS HETEROCICLICOS Y USO FARMACÉUTICO DE 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
Carrera 9 No 93-09 – Bogotá, D C
Teléfonos 6107420 – 6107480


Margarita Castellanos Abondano
C C No 39.779.654 de Usaquén
T P A No 70 819 del C S J
Carrera 9 No 93-09 – Bogotá, D C
Teléfonos 6107420 – 6107480

Bogotá, D C
XCA/MCA/4906-FNPCT



AUTENTICACION DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
(Art. 84 C RC mod. Decr. 2282 de 1989, art. 1 mod. 38)
Ante el Notario Cuarenta y Uno (41) del circulo de esta ciudad compareció personalmente:
María Cely Castellón
Identificado con C.C. *39779657* y tarjeta profesional expedida en *USA* y tarjeta profesional del Consejo Superior de la Judicatura, con documento de identidad *Supermin*
y declaró que la firma puesta en este escrito es suya.
María Cely Castellón
Firma del declarante
En Bogotá D.C. a *26 DIC 2003*
AUTORIZÓ ESTA DILIGENCIA EL SUSCRITO NOTARIO



AUTENTICACION DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
(Art. 84 C RC mod. Decr. 2282 de 1989, art. 1 mod. 38)
Ante el Notario Cuarenta y Uno (41) del circulo de esta ciudad compareció personalmente:
Margarita Cely Castellón
Identificado con C.C. *39779657* y tarjeta profesional expedida en *USA* y tarjeta profesional del Consejo Superior de la Judicatura, con documento de identidad *Supermin*
y declaró que la firma puesta en este escrito es suya.
Margarita Cely Castellón
Firma del declarante
En Bogotá D.C. a *26 DIC 2003*
AUTORIZÓ ESTA DILIGENCIA EL SUSCRITO NOTARIO

PODER

El (los) suscrito (s) _____
Kyoto Pharmaceutical Industries, Ltd.

domiciliado (s) en 38, Nishinokyo Tsukinowa-cho,
Nakakyo-ku, Kyoto-shi, Kyoto 604-8444,
JAPON

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

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

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

Dado y firmado hoy 1° de Diciembre del 2003

en Kyoto, Japón

Por Kyoto Pharmaceutical Industries, Ltd.
Kazuhiko KITAO - Representante

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

POWER OF ATTORNEY

I (we) the undersigned Kyoto Pharmaceutical Industries, Ltd

of 38, Nishinokyo Tsukinowa-cho, Nakakyo-ku,
Kyoto-shi, Kyoto 604-8444 Japan

hereby grants Power of Attorney to XIMENA CASTELLANOS A. and/or
MARGARITA CASTELLANOS A. attorneys residing at Carrera 9 No. 93-09
Bogotá - COLOMBIA to _____

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

a) Obtention of patents, models and designs; registration of trademarks,
service, collective and defensive marks, and of designations of origin; the
deposit of commercial names and ensigns; its renewal, extension, recordal
of assignments, change of name or domicile, voluntary cancellation; and the
registration of licenses of use of the above rights; b) For the obtention of
Sanitary Registrations; c) Actions of opposition, cancellation, nullity,
infringement, granting of licenses; and in general the civil, criminal and
administrative suits related to those 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 in fact, in or out of Court
given and signed this 1st day of December, 2003

In Kyoto, Japan

By Kyoto Pharmaceutical Industries, Ltd.

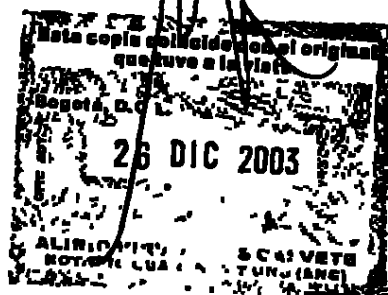
Kazuhiko Kitao

(Notary should execute on other side)
(Consular legalization necessary)
Kazuhiko KITAO
Representative Director
and President

ALVARO CASTELLANOS M. & CIA.

ABOGADOS COLOMBIA

Carrera 9 No. 93-09 - P.O. Box 4349 - Bogotá, Colombia.
Tels. (571) 610 7420 / 60 / 80 - Fax. (571) 610 0706 - e-mail: acastell@impasat.net.co



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1 Country JAPAN

This public document

2 has been signed by Shunichi TAKEUCHI

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

4 bears the seal/stamp of Shunichi TAKEUCHI, Notary Public

Certified

5 at Osaka

6 DEC - 4. 2003

7 by the Ministry of Foreign Affairs

8 No 04221

9 Seal/stamp



10 Signature

Tsutomu HIGUCHI

For the Minister for Foreign Affairs





俊人

8

登簿番号平成15年第 558 号

囑託人は日本の法律の下に合法的に設立され
存在している、604-8444日本国京都府
京都市中京区西ノ京月輪町38番地に所在する
京都薬品工業株式会社代表取締役であり
添付の書類に署名する権限を有している北尾和彦
の代理人寺前美智子は当公証人の面前で
この委任状にある上記囑託人の署名
を自認した。 _____

よってこれを認証する。 _____

平成15年12月3日

当公証人役場において _____

大阪市中央区平野町2丁目1番2号(沢の鶴ビル内)

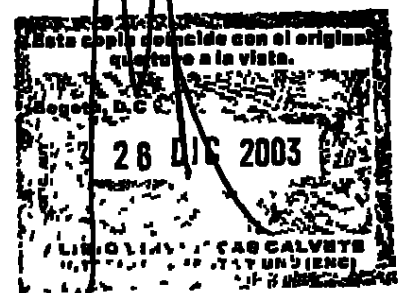
大阪法務局所属

公証人

竹内俊一



大阪法務局所属 公証人役場



Registered No. 558 - 2003

NOTARIAL CERTIFICATE

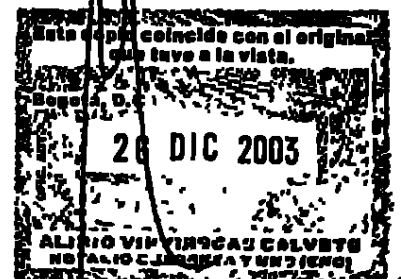
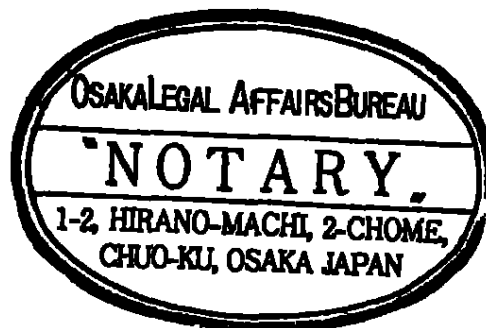
This is to certify that Michiko TERAMAE, an agent of Mr Kazuhiko KITAO, Representative Director and President of Kyoto Pharmaceutical Industries, Ltd being legally constituted and existing under the laws of Japan and located at 38, Nishinokyo Tsukinowa-cho, Nakakyo-ku, Kyoto-shi, Kyoto 604-8444 Japan, who is entitled to sign the attached document, has stated in my very presence that the said Mr. Kazuhiko KITAO acknowledged himself to have signed to the attached document.

Dated this 3rd day of December, 2003

Shunichi Takouchi

NOTARY

Osaka Legal Affairs Bureau
1-2, Hirano-machi 2-chome
Chuo-ku, Osaka Japan





總第 2773 号



証 明

大阪法務局所属公証人 竹内 俊一

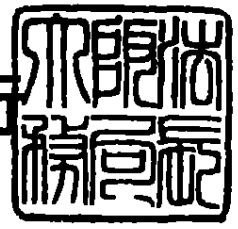
平成 15 年 12 月 3 日付

平成 15 年 登録 第 558 号

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

平成 15 年 12 月 4 日
平成 年 月 日

大阪法務局長 小池 信行

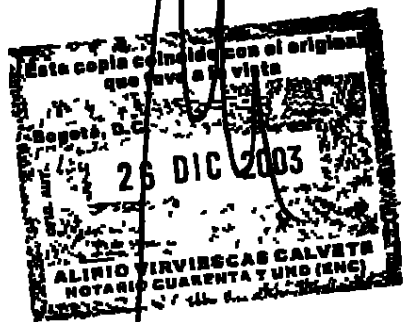


CERTIFICATE

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

Date 03.12.4

Director of the Osaka Legal Affairs Bureau



HB
11

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

(Anexo a documento de Poder de Kyoto Pharmaceutical Industries, Ltd.)

Registro No. 558-2003

CERTIFICADO NOTARIAL

La presente es para certificar que Michiko TERAMAE, agente del señor Kazuhiko KITAO, Director Representante y Presidente de Kyoto Pharmaceutical Industries, Ltd. La cual está legalmente constituida y existe bajo las leyes del Japón y está domiciliada en el No. 38 Nishinokyo Tsukinowa-cho, Nakakyo-ku, Kyoto-shi, Kyoto 604-8444 Japón, quien tiene derecho a firmar el documento adjunto ha manifestado en mi propia presencia que dicho señor Kazuhiko KITAO reconoció el mismo haber firmado el documento adjunto.

Dado hoy día 3 de Diciembre, 2003.

(fdo) ilegible

NOTARIO

Oficina de Asuntos legales de Osaka

1-2, Hirano-machi 2-chome

Chuo-ku, Osaka, Japón

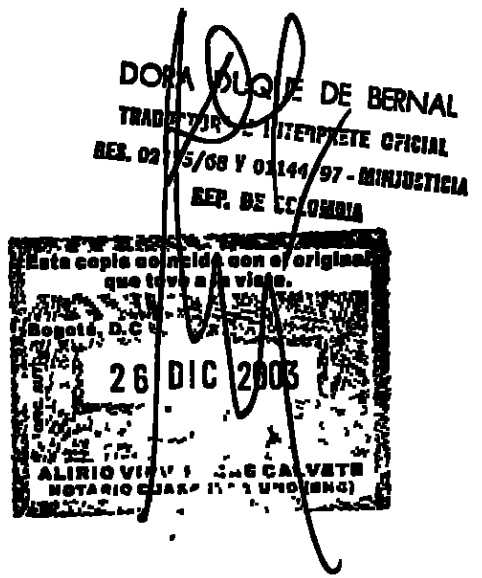
(Sello):

Oficina de Asuntos Legales de Osaka

NOTARIO

1-2 Hirano-machi, 2-chome

Chuo-ku, Osaka, Japón



12
12

CERTIFICADO

La presente es para certificar que la firma que aparece anteriormente ha sido
impuesta por Notario, debidamente autorizado por la Oficina de Asuntos Legales
de Tokyo y que el sello oficial que aparece en el mismo es auténtico.

Fecha: 03-12-4

Director de la Oficina de Asuntos legales de Osaka

APOSTILLA

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

1. País: JAPON

Este documento público

2. ha sido firmado por Shunichi TAKEUCHI

3. actuando en su carácter de Notario Público de la Oficina de Asuntos legales
de Osaka

4. lleva el sello de Shunichi TAKEUCHI, Notario Público

Certificado

5. en Osaka

6. El 4 de Diciembre de 2003

7. por el Ministerio de Relaciones Exteriores

8. No. 04221

9. Sello

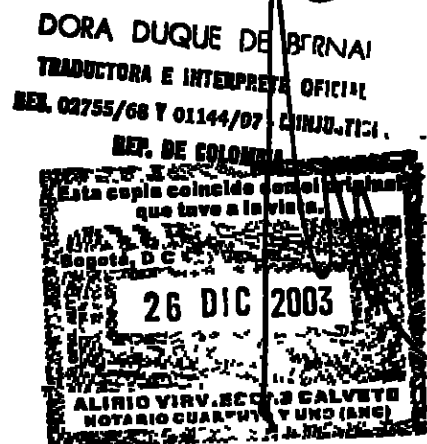
10. Firma

(fdo) Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

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

[Handwritten signature]



JEFE DE REALIZACIONES
SANTAFÉ DE BOGOTÁ D.C.
2003
2003 DEC 15 A 11 11
RESPONSABILIDAD DEL TEXTO
NO SE ASUME

ALISTADO DE RELACIONES
PRENDADES
08.5.3
CUYA FIRMA APARECE EN EL
DOCUMENTO RESPECTIVO
LAS FIRMAS DE LOS PRENDADES

Esta copia coincide con el original
que tiene a la vista.
26 DIC 2003
ALFONSO VILLALBA
NOTARIO

P A T E N T S

CESION

El (los) suscritor (s)
Hiroshi MATSUI, Hideo KOBAYASHI,
Satoru AZUKIZAWA, Masayasu KASAI,
Akihisa YOSHIMI y Hiroaki SHIRAHASE

en consideración al pago de la suma de
(...US\$ 1.00 ...), que he(mos)
recibido, por el presente documento cedo
(cedemos) a

Kyoto Pharmaceutical Industries, Ltd.

una compañía constituida de conformidad con las
leyes de Japón

con oficinas en
38, Nishinokyo Tsukinowa-cho, Nakakyo-ku
Kyoto-shi, Kyoto 604-8444 Japón

todos los derechos y títulos sobre la invención
denominada

"NUEVOS COMPUESTOS HETEROCICLICOS Y USO
FARMACEUTICO DE LOS MISMOS"

EL CESIONARIO firma también el presente y
declara que acepta dicha cesión

Dado y firmado hoy 1° de Diciembre del 2003

en Kyoto, Japón

ASSIGNMENT

The undersigned

Hiroshi MATSUI, Hideo KOBAYASHI,
Satoru AZUKIZAWA, Masayasu KASAI,
Akihisa YOSHIMI and Hiroaki SHIRAHASE

In consideration of the sum of
(US\$ 1.00), the receipt of which
is hereby acknowledged, by these presents do sell,
assign and transfer unto

Kyoto Pharmaceutical Industries, Ltd

a corporation organized under the laws of
Japan

having a place of business at
38, Nishinokyo Tsukinowa-cho, Nakakyo-ku,
Kyoto-shi, Kyoto 604-8444 Japan

all rights and title to the invention related to

NOVEL HETEROCYCLIC COMPOUND AND
MEDICINAL USE THEREOF

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

Given and signed this 1st day of December, 2003

In Kyoto, Japan

Inventors

Hiroshi Matsui
Hiroshi MATSUI

Hideo Kobayashi
Hideo KOBAYASHI

Satoru Azukizawa
Satoru AZUKIZAWA

Masayasu Kasai
Masayasu KASAI

Akihisa Yoshimi
Akihisa YOSHIMI

Hiroaki Shirahase
Hiroaki SHIRAHASE

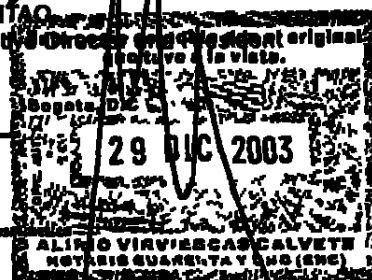
Assignee

Kazuhiko Kitao
Kazuhiko KITAO
Representative

ALVARO CASTELLANOS M. & CIA.

ABOGADOS COLOMBIA

Carrera 9 No. 93-89- P.O.Box 8349 - Bogotá, Colombia
Tels (371) 610 74 20 / 80 / 80 - Fax (371) 610 87 84 - e-mail: acastellanos@bogota.com.co



ALVARO CASTELLANOS M. & CIA. ABOGADOS COLOMBIA



APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1 Country JAPAN

This public document

2 has been signed by Shunichi TAKEUCHI

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

4 bears the seal/stamp of Shunichi TAKEUCHI Notary Public

Certified

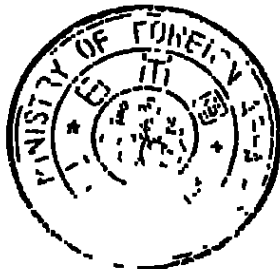
5 at Osaka

6 DEC - 4 2003

7 by the Ministry of Foreign Affairs

8 No 04224

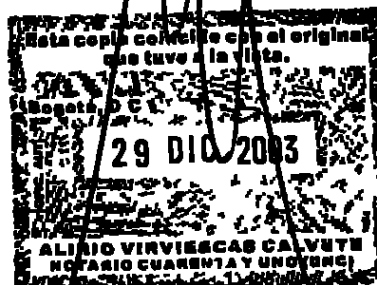
9 Seal/Stamp



10 Signature

Tsutomu HIGUCHI

For the Minister for Foreign Affairs



12/3

後人

12/3



登簿番号平成15年第 561 号

囑託人松井博、小林英夫、小豆澤智、笠井正恭、
吉見彰久、白波瀬弘明の代理人寺前美智子は
当公証人の面前でこの譲渡証書にある
上記囑託人の署名を自認した。
よってこれを認証する。

平成15年12月3日

当公証人役場において

大阪市中央区平野町2丁目1番2号(沢の鶴ビル内)

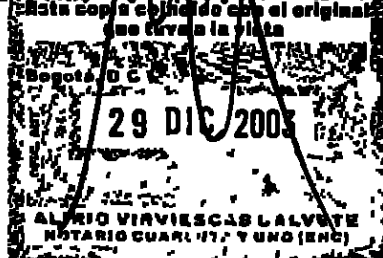
大阪法務局所属

公証人

竹内俊一



大阪法務局所属公証人役場





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Registered No 561 -2003

NOTARIAL CERTIFICATE

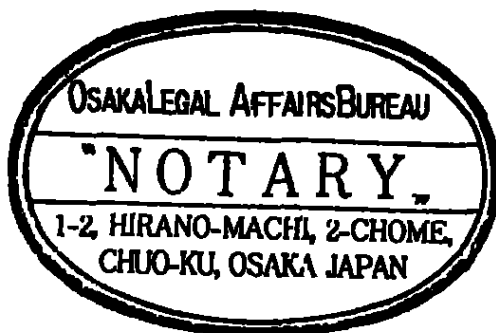
This is to certify that Michiko TERAMAE, an agent of Mr Hiroshi MATSUI, Mr Hideo KOBAYASHI, Mr Satoru AZUKIZAWA, Mr Masayasu KASAI, Mr. Akihisa YOSHIMI and Mr Hiroaki SHIRAHASE has stated in my very presence that the said Mr Hiroshi MATSUI, Mr Hideo KOBAYASHI, Mr Satoru AZUKIZAWA, Mr Masayasu KASAI, Mr. Akihisa YOSHIMI and Mr. Hiroaki SHIRAHASE acknowledged themselves to have signed to the attached document

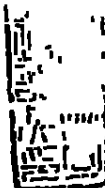
Dated this 3rd day of December, 2003

Akunishi Takashi

NOTARY

Osaka Legal Affairs Bureau
1-2, Hirano-machi 2-chome
Chuo-ku, Osaka Japan





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總第 2776 号

証 明

大阪法務局所属公証人

竹内俊一

平成 15 年 12 月 3 日 付

平成 15 年 登録 第 561 号

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

平成 15 年 12 月 4 日

平成 年 月 日

大阪法務局長

小池信行

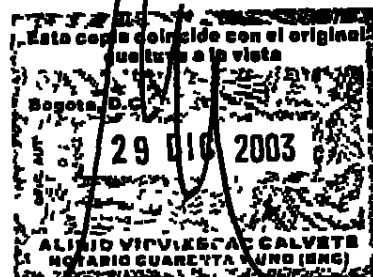


CERTIFICATE

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

Date 03.12.4

Director of the Osaka Legal Affairs Bureau



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_____**TRADUCCION OFICIAL No 03-1208**_____

de un documento escrito en INGLÉS, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial, Res 2755/88 y 01144/97 de Minjusticia, al igual que la presente._____

(Anexo a documento de cesión de Hiroshi MATSUI, Hideo KOBAYASHI, Satoru AZUKIZAWA, Masayasu KASAI, Akihisa YOSHIMI e Hiroaki SHIRAHASE)

Registro No 561-2003

CERTIFICADO NOTARIAL

La presente es para certificar que Michiko TERAMAE, agente del señor Hiroshi MATSUI, señor Hideo KOBAYASHI, señor Satoru AZUKIZAWA, señor Masayasu KASAI, señor Akihisa YOSHIMI y señor Hiroaki SHIRAHASE ha manifestado en mi propia presencia que el señor Hiroshi MATSUI, señor Hideo KOBAYASHI, señor Satoru AZUKIZAWA, señor Masayasu KASAI, señor Akihisa YOSHIMI y señor Hiroaki SHIRAHASE reconocieron ellos mismos haber firmado el documento adjunto

Dado hoy día 3 de Diciembre, 2003

(fdo) ilegible

NOTARIO

Oficina de Asuntos legales de Osaka

1-2, Hirano-machi 2-chome

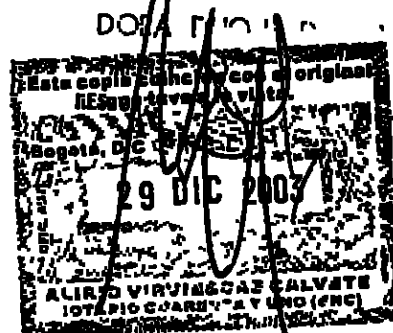
Chuo-ku, Osaka, Japón

(Sello).

Oficina de Asuntos Legales de Osaka

NOTARIO

1-2 Hirano-machi, 2-chome



Chuo-ku, Osaka, Japón

CERTIFICADO

La presente es para certificar que la firma que aparece anteriormente ha sido
impuesta por Notario, debidamente autorizado por la Oficina de Asuntos Legales
de Tokyo y que el sello oficial que aparece en el mismo es auténtico

Fecha: 03-12-4

Director de la Oficina de Asuntos legales de Osaka

APOSTILLA

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

1 País: JAPON

Este documento público

2. ha sido firmado por Shunichi TAKEUCHI

3. actuando en su carácter de Notario Público de la Oficina de Asuntos legales
de Osaka

4. lleva el sello de Shunichi TAKEUCHI, Notario Público

Certificado

5. en Osaka

6. El 4 de Diciembre de 2003

7 por el Ministerio de Relaciones Exteriores

8. No 04224

9. Sello:

10. Firma

(fdo) Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores.

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

[Handwritten signature]

DORA FUQUE DE P...
TRADUC...
NEZ. 02755 Esta copia certificada con el original
que tiene a la vista
SECRETARÍA DE...
BOGOTÁ, D.C.
29 DIC 2003
ALIRIO VIRVEZCAS CALUETE
NOTARIO GLADIATA Y UNO (NGC)

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(12) 許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局(43) 国際公開日
2002年12月5日 (05.12.2002)

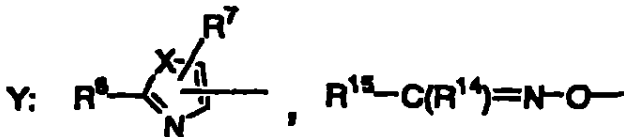
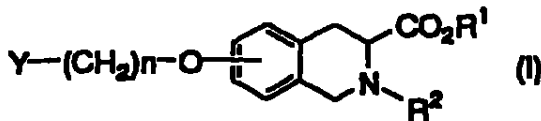
PCT

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第2001-161489号 2001年5月29日 (29.05.2001) JP
- (71) 出願人 (米国を除く全ての指定国について): 京都薬品工業株式会社 (KYOTO PHARMACEUTICAL INDUSTRIES, LTD.) [JP/JP], 〒604-8444 京都府京都市中京区西ノ京月輪町3番地 Kyoto (JP)
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- (81) 指定国 (国内): AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GR, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
- (84) 指定国 (広域): ARIPO 特許 (GI, GM, HE, IS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IT, LU, MC, NL, PT, SE, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- 付公開書類
国際調査報告書
- 2文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title. NOVEL HETEROCYCLIC COMPOUND AND MEDICINAL USE THEREOF

(54) 発明の名称 新規複素環化合物およびその医薬用途



(57) Abstract A novel heterocyclic compound which is either one represented by the formula (I) (I) {wherein R^1 represents hydrogen or C_{1-4} alkyl, R^2 represents hydrogen, $-\text{CO}-C(R^4)=C(R^4)-R^1$ (wherein R^4 is hydrogen or C_{1-4} alkyl and R^5 is C_{2-4} alkyl, C_{2-4} alkenyl, etc.), etc. Y represents a group represented by (II) {wherein X is oxygen or sulfur, R^7 has the same meaning as R^1 , R^8 is $R^{15}-C(R^{14})=C(R^{14})-$ (wherein R^{14} has the same meaning as R^4 and R^{15} is C_{2-4} alkyl, etc.), etc., R^{14} has the same meaning as R^4 , and R^{15} represents aryl, etc.} $Y-(CH_2)_n-O-$ is bonded to the 6- or 7-position carbon atom of the tetrahydroquinoline skeleton, and n is an integer of 1 to 4,

or a pharmaceutically acceptable salt thereof. The compound (I) is useful as an antihyperglycemic agent, antihyperlipemic agent, insulin resistance ameliorant, diabetes remedy, remedy for complications of diabetes, glucose tolerance insufficiency ameliorant, antiarteriosclerotic agent, antiobese agent, anti-inflammatory agent, preventive/remedy for diseases attributable to PPAR, and preventive/remedy for X syndrome.

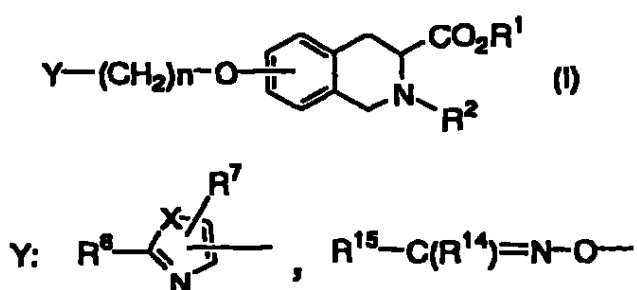
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(57) 要約

本発明にかかる新規複素環化合物は、式 (I)



{式中、 R^1 はH又は C_{1-8} アルキル、 R^2 はH、 $-CO-C(R^4)=C(R^4)-R^5$ (式中、 R^4 はH又は C_{1-4} アルキル、 R^5 は C_{4-8} アルキル、 C_{2-8} アルケニル等)等、 Y は下記の基 [式中、 X はO、S、 R^7 は R^4 と同義、 R^8 は $R^{10}-C(R^9)=C(R^9)-$ (式中、 R^9 は R^4 と同義、 R^{10} は C_{3-8} アルキル等)等、 R^{14} は R^4 と同義、 R^{15} はアリール等を示す]を示し、 $Y-(CH_2)_n-O-$ はテトラヒドロイソキノリン骨格の6又は7位に結合し、 n は1-4の整数を示す}で表される新規複素環化合物又はその医薬上許容される塩である。本発明の化合物(I)は、抗高血糖剤、抗高脂血症剤、インスリン抵抗性改善剤、糖尿病治療剤、尿病合併症治療剤、耐糖能不全改善剤、抗動脈硬化症剤、抗肥満症剤、抗炎症剤、PPAR媒介疾患の予防・治療剤およびX症候群の予防・治療剤として有用である。

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SPECIFICATION

NOVEL HETEROCYCLIC COMPOUND AND MEDICINAL USE THEREOF

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel heterocyclic
5 compound and a pharmaceutically acceptable salt thereof, which
have a hypoglycemic action, a blood hypolipidemic action, an
insulin resistance-improving action and a PPAR (peroxisome
proliferator-activated receptor)-activating action. The
present invention also relates to a pharmaceutical composition
10 comprising the above-mentioned novel heterocyclic compound or a
pharmaceutically acceptable salt thereof. Furthermore, the
present invention relates to a hypoglycemic agent, a
hypolipidemic agent, an insulin resistance improver, a
therapeutic agent of diabetes, a therapeutic agent of diabetic
15 complications, a glucose tolerance improver, an anti-
arteriosclerosis agent, an anti-obesity agent, an
antiinflammatory agent, an agent for the prophylaxis or
treatment of PPAR-mediated diseases and an agent for the
prophylaxis or treatment of syndrome X, all of which comprising
20 the above-mentioned novel heterocyclic compound or a
pharmaceutically acceptable salt thereof.

BACKGROUND OF THE INVENTION

As a therapeutic agent of diabetes, biguanide compounds
having, as a main action, an inhibitory action on glucose
25 absorption via the intestinal tract and on glucose release from
the liver, sulfonylurea compounds having an accelerating action
on insulin secretion as a main action, insulin and the like
have been employed. However, biguanide compounds cause lactic
acidosis, and sulfonylurea compounds sometimes cause serious
30 hypoglycemia due to their strong hypoglycemic action.
Therefore, a due care should be given when in use of these
compounds. In recent years, there have been active researches
and developments of a therapeutic agent of diabetes, which is

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free of these defects, with the consequence that various compounds having an insulin resistance-improving action have been found.

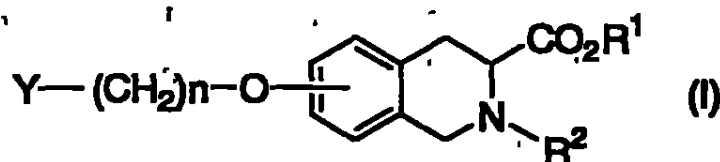
The insulin resistance plays an important role as a cause
5 of non-insulin dependent diabetes mellitus (NIDDM), along with decrease in the insulin secretion. As an agent that improves insulin resistance, various thiazolidine compounds are known. Examples of such compound include 5-[4-[(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy]benzyl]-2,4-thiazolidinedione
10 (general name: troglitazone) is described in USP 4572912 and EP0139421B1, 5-[[4-[2-(5-ethyl-pyridin-2-yl)ethoxy]phenyl]-methyl]-2,4-thiazolidinedione (general name: pioglitazone) is described in USP4687777 and EP0193256B1, and 5-[[4-[2-[N-methyl-N-(pyridin-2-yl)amino]ethoxy]phenyl]methyl]-2,4-
15 thiazolidinedione (general name: rosiglitazone) is described in USP5002953 and EP0306228B1. However, these pharmaceutical agents that improve insulin resistance may cause side effects such as hepatopathy, retention of fluid, edema, megalocardia, obesity and the like. Thus, the development of a highly safe
20 insulin resistance improver effective for NIDDM has been desired.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a compound having a hypoglycemic action, a blood
25 hypolipidemic action, an insulin resistance-improving action and a PPAR activating action, which has a structure completely different from that of conventional compounds and which is highly safe, thereby to increase the diversity in and to broaden the range of selection from hypoglycemic agents, hypolipidemic agents, insulin resistance improvers, therapeutic
30 agents of diabetes, therapeutic agents of diabetic complications, glucose tolerance improvers, anti-arteriosclerosis agents, anti-obesity agents, antiinflammatory

agents, agents for the prophylaxis or treatment of PPAR-mediated diseases and agents for the prophylaxis or treatment of syndrome X.

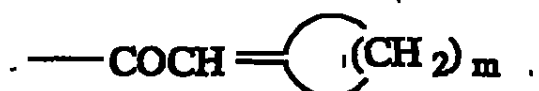
The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a novel heterocyclic compound of the formula (I)



wherein

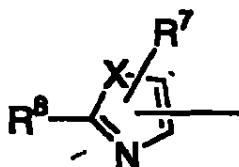
R^1 is a hydrogen atom or C_{1-6} alkyl;

R^2 is a hydrogen atom, $-\text{CO}-R^3$ wherein R^3 is C_{2-6} alkyl optionally substituted by halogen, $-\text{CO}-\text{C}(R^4)=\text{C}(R^4)-R^5$ wherein R^4 is optionally the same as the other R^4 and is a hydrogen atom or C_{1-4} alkyl, and R^5 is C_{1-3} alkyl, C_{2-3} alkenyl, aryl or aromatic heterocycle, $-\text{CO}-\text{C}=\text{C}-R^6$ wherein R^6 is C_{1-3} alkyl,



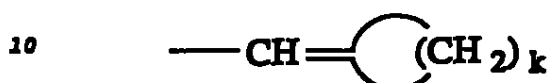
wherein m is an integer of 2 to 7, aryl, optionally substituted aryl C_{1-3} alkyl, C_{1-6} alkyl optionally substituted by halogen, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{3-6} cycloalkyl C_{1-3} alkyl;

Y is



wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is C_{3-6} alkyl, C_{4-6} cycloalkyl, C_{1-4} alkylthio C_{1-6} alkyl, $R^{10}-\text{C}(R^9)=\text{C}(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl and R^{10} is

C₁₋₆ alkyl optionally substituted by halogen, C₂₋₆ alkenyl, aryl, an aromatic heterocyclic, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₃ alkyl, C₁₋₄ alkoxy C₁₋₆ alkyl, C₁₋₄ alkylthio C₁₋₆ alkyl or C₁₋₆ alkyl substituted by (R⁹)₂N- wherein R⁹ is optionally the same as the other R⁹ and is a hydrogen atom or C₁₋₄ alkyl, R¹²-CO-N(R¹¹)- wherein R¹¹ is a hydrogen atom or C₁₋₄ alkyl and R¹² is C₁₋₆ alkyl or aryl, R¹³-Z- wherein R¹³ is C₁₋₆ alkyl or aryl and Z is an oxygen atom or a sulfur atom, or



wherein k is an integer of 2 to 7 and X is an oxygen atom or a sulfur atom, or

R¹⁵-C(R¹⁴)-N-O- wherein R¹⁴ is a hydrogen atom or C₁₋₄ alkyl and R¹⁵ is aryl or an aromatic heterocycle;

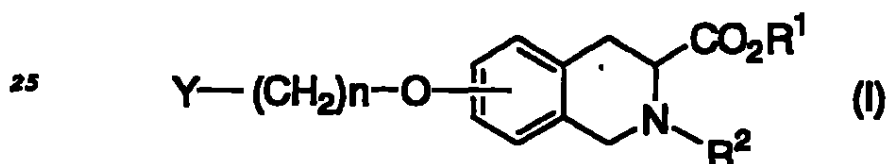
Y-(CH₂)_n-O- is bonded to the 6- or 7-position of a tetrahydroisoquinoline skeleton; and

n is an integer of 1 to 4

and a pharmaceutically acceptable salt thereof have a hypoglycemic action, a blood hypolipidemic action, an insulin resistance-improving action and a PPAR activating action, as well as high safety.

Accordingly, the present invention provides the following.

[1] A novel heterocyclic compound of the formula (I)



wherein

R¹ is a hydrogen atom or C₁₋₆ alkyl;

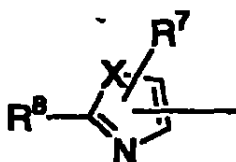
R² is a hydrogen atom, -CO-R³ wherein R³ is C₂₋₆ alkyl optionally substituted by halogen, -CO-C(R⁴)=C(R⁴)-R⁵

wherein R^4 is optionally the same as the other R^4 and is a hydrogen atom or C_{1-4} alkyl, and R^5 is C_{1-8} alkyl, C_{2-8} alkenyl, aryl or an aromatic heterocycle, $-\text{CO}-\text{C}_m\text{C}-R^6$ wherein R^6 is C_{1-8} alkyl,

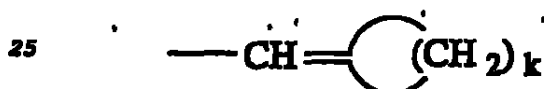


wherein m is an integer of 2 to 7, aryl, optionally substituted aryl C_{1-3} alkyl, C_{1-6} alkyl optionally substituted by halogen, C_{2-6} alkenyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkyl C_{1-3} alkyl;

10 Y is



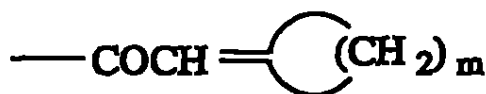
wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is C_{3-8} alkyl, C_{4-8} cycloalkyl, C_{1-4} alkylthio C_{1-6} alkyl, $R^{10}-\text{C}(R^9)-\text{C}(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl and R^{10} is C_{1-6} alkyl optionally substituted by halogen, C_{2-8} alkenyl, aryl, an aromatic heterocycle, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl, C_{1-4} alkoxy C_{1-6} alkyl, C_{1-4} alkylthio C_{1-6} alkyl or C_{1-6} alkyl substituted by $(R^9)_2\text{N}-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl, $R^{12}-\text{CO}-\text{N}(R^{11})-$ wherein R^{11} is a hydrogen atom or C_{1-4} alkyl and R^{12} is C_{1-6} alkyl or aryl, $R^{13}-Z-$ wherein R^{13} is C_{1-8} alkyl or aryl and Z is an oxygen atom or a sulfur atom, or



wherein k is an integer of 2 to 7 and X is an oxygen atom or a sulfur atom, or

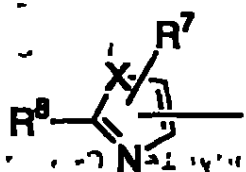
$R^{15}-C(R^{14})=N-O-$ wherein R^{14} is a hydrogen atom or C_{1-4} alkyl
 and R^{15} is aryl or an aromatic heterocycle;
 $Y-(CH_2)_n-O-$ is bonded to the 6- or 7-position of a
 tetrahydroisoquinoline skeleton; and
 n is an integer of 1 to 4,
 or a pharmaceutically acceptable salt thereof.

[2] The novel heterocyclic compound of [1] above, wherein, in
 the formula (I), R^2 is an optionally substituted aryl C_{1-3} alkyl,
 C_{1-6} alkyl optionally substituted by halogen, C_{2-6} alkenyl, C_{3-8}
 cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl or

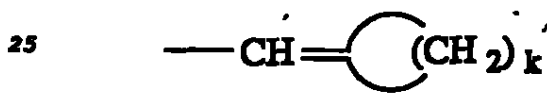


wherein m is an integer of 2 to 7, or a pharmaceutically
 acceptable salt thereof.

[3] The novel heterocyclic compound of [1] above, wherein, in
 the formula (I), Y is



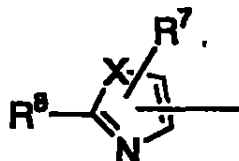
wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is C_{1-4} alkylthio
 C_{1-6} alkyl, $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as
 the other R^9 and is a hydrogen atom or C_{1-4} alkyl, R^{10} is C_{1-6}
 alkyl optionally substituted by halogen, C_{3-8} cycloalkyl, C_{3-8}
 cycloalkyl C_{1-3} alkyl, C_{1-4} alkoxy C_{1-6} alkyl, C_{1-4} alkylthio C_{1-6}
 alkyl, C_{1-6} alkyl substituted by, $(R^9)_2N-$ wherein R^9 is optionally
 the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl,
 or



wherein k is an integer of 2 to 7, and X is an oxygen atom or a

sulfur atom, or a pharmaceutically acceptable salt thereof.

- [4] The novel heterocyclic compound of [1] above, wherein, in the formula (I), R^2 is a hydrogen atom, $-CO-R^3$ wherein R^3 is C_{2-6} alkyl optionally substituted by halogen, $-COC(R^4)=C(R^4)-R^5$ wherein R^4 is optionally the same as the other R^4 and is a hydrogen atom or C_{1-4} alkyl and R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, aryl or aromatic heterocycle, $-CO-C=C-R^6$ wherein R^6 is C_{1-6} alkyl, or aryl, Y is

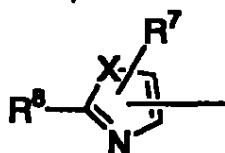


- wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is C_{3-6} alkyl, C_{4-6} cycloalkyl, $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl, R^{10} is C_{1-6} alkyl, C_{2-6} alkenyl, aryl or aromatic heterocycle, $R^{12}-CO-N(R^{11})-$ wherein R^{11} is a hydrogen atom or C_{1-4} alkyl, and R^{12} is C_{1-6} alkyl or aryl, or $R^{13}-Z-$ wherein R^{13} is C_{1-6} alkyl or aryl and Z is an oxygen atom or a sulfur atom, and X is an oxygen atom or a sulfur atom, or $R^{15}-C(R^{14})=N-O-$ wherein R^{14} is a hydrogen atom or C_{1-4} alkyl and R^{15} is aryl or aromatic heterocycle, or a pharmaceutically acceptable salt thereof.

- [5] The novel heterocyclic compound of [2] or [3] above, wherein, in the formula (I), $Y-(CH_2)_n-O-$ is bonded to the 7-position of a tetrahydroisoquinoline skeleton and n is 2, or a pharmaceutically acceptable salt thereof.

- [6] The novel heterocyclic compound of [4] above, wherein, in the formula (I), $Y-(CH_2)_n-O-$ is bonded to the 7-position of a tetrahydroisoquinoline skeleton and n is 2, or a pharmaceutically acceptable salt thereof.

[7] The novel heterocyclic compound of [6] above, wherein, in the formula (I), Y is

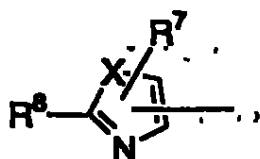


wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is R^{10} -

5 $C(R^9)-C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl, and R^{10} is C_{1-6} alkyl, C_{2-6} alkenyl or aryl, or a pharmaceutically acceptable salt thereof.

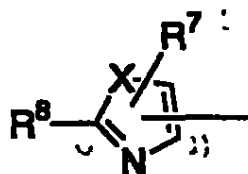
[8] The novel heterocyclic compound of [6] above, wherein, in the formula (I), Y is

10



wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is $R^{13}-Z-$ wherein R^{13} is C_{1-6} alkyl or aryl, and Z is a sulfur atom, or a pharmaceutically acceptable salt thereof.

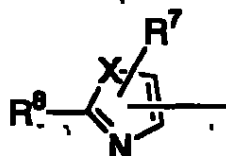
15 [9] The novel heterocyclic compound of [6] above, wherein, in the formula (I), Y is



wherein R^7 is a hydrogen atom or C_{1-4} alkyl and R^8 is C_{3-6} alkyl or C_{4-6} cycloalkyl, or a pharmaceutically acceptable salt thereof.

20 [10] The novel heterocyclic compound of [5] above, wherein, in the formula (I), Y is

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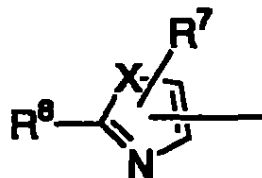


wherein R^7 is a hydrogen atom or C_{1-4} alkyl and R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl and R^{10} is C_{3-8} cycloalkyl, or a pharmaceutically acceptable salt thereof.

[11] The novel heterocyclic compound of any of [7] to [10] above, wherein, in the formula (I), R^2 is $-CO-C(R^4)-C(R^4)-R^5$ wherein R^4 is a hydrogen atom and R^5 is C_{1-3} alkyl or C_{2-3} alkenyl, or a pharmaceutically acceptable salt thereof.

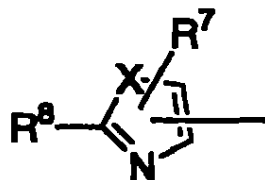
[12] The novel heterocyclic compound of any of [7] to [10] above, wherein, in the formula (I), R^2 is $-CO-C-C-R^6$ wherein R^6 is C_{1-3} alkyl, or a pharmaceutically acceptable salt thereof.

[13] The novel heterocyclic compound of [6] above, wherein, in the formula (I), Y is



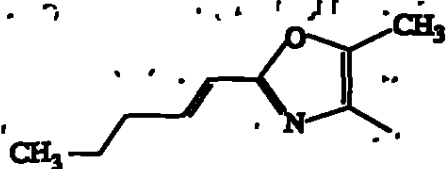
wherein R^7 is C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl and R^{10} is C_{1-6} alkyl, and X is an oxygen atom, or a pharmaceutically acceptable salt thereof.

[14] The novel heterocyclic compound of [6] above, wherein, in the formula (I), Y is

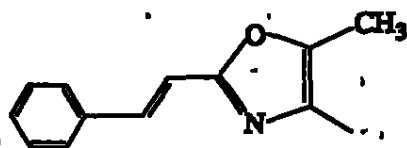


wherein R^7 is C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is a hydrogen atom and R^{10} is aryl, and X is an oxygen atom, or a pharmaceutically acceptable salt thereof.

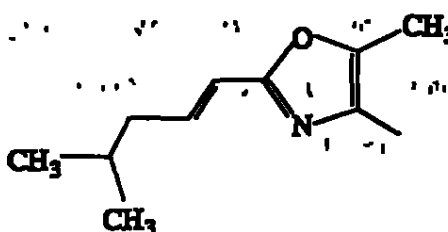
[15] The novel heterocyclic compound of [4] or [5] above, wherein, in the formula (I), Y is selected from the following (a) to (n):



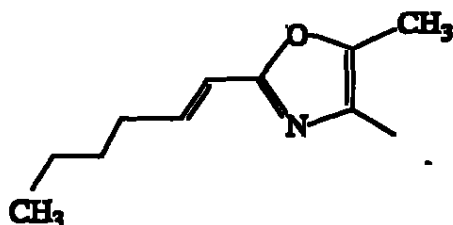
(a)



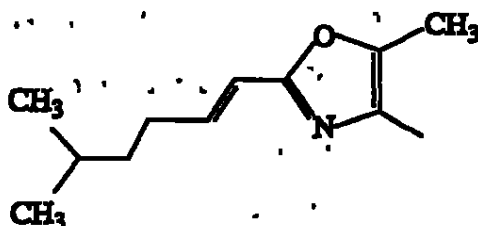
(b)



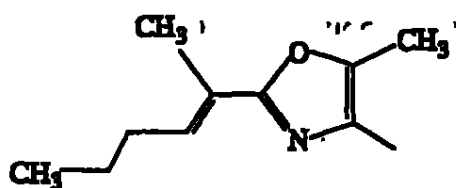
(c)



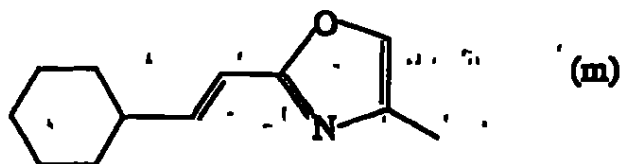
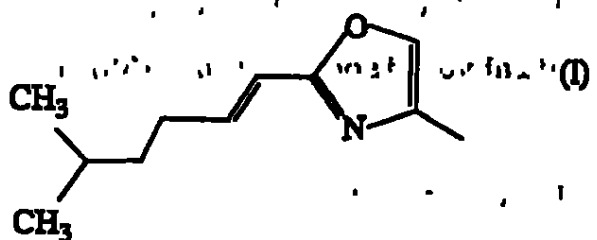
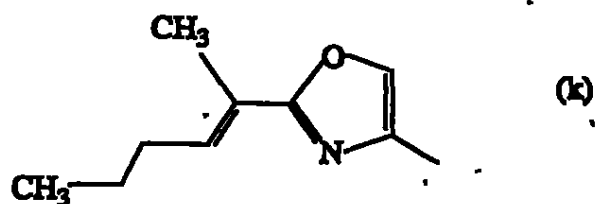
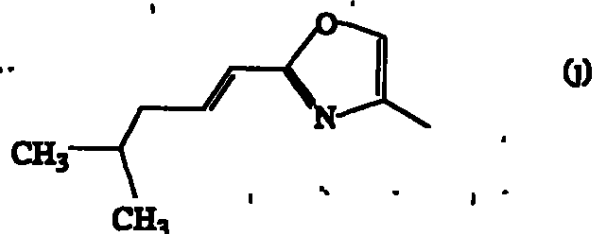
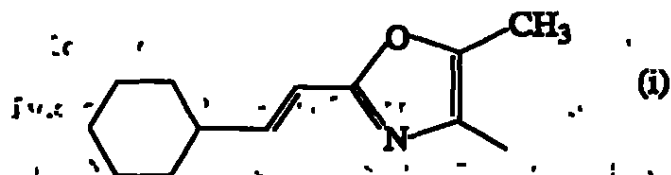
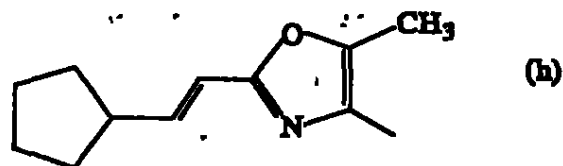
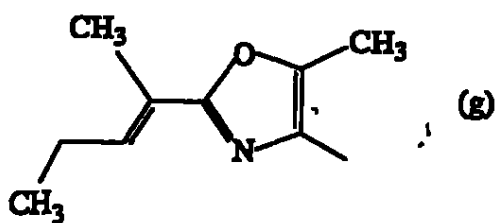
(d)



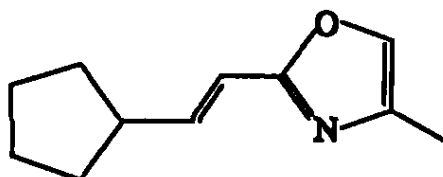
(e)



(f)



and



(n)

or a pharmaceutically acceptable salt thereof

[16] The novel heterocyclic compound of [1] above, wherein the compound of the formula (I) is any of the following (1) to

5 (16):

(1) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(2) 2-(2-heptenoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

10 (3) 2-(2-hexynoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(4) 7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-2-pentafluoropropionyl-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

15 (5) 2-(2-heptenoyl)-7-[2-(5-methyl-2-styrylthiazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(6) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

20 (7) 2-(2-heptenoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(8) 2-(2-hexynoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(9) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(1,3-pentadien-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(10) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-pentyloxazol-4-

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yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
(11) 7-[2-(2-cyclopentyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(12) 7-[2-(2-cyclohexyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(13) 7-[2-(2-benzoylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(14) 7-[2-(2-butyrylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(15) 2-(2-heptenoyl)-7-[2-(4-methyl-2-phenylsulfanylthiazol-5-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
and

(16) 2-(2-heptenoyl)-7-[2-(1-phenylethylideneaminoxy)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
or a pharmaceutically acceptable salt thereof.

[17] The novel heterocyclic compound of [1] above, wherein the compound of the formula (I) is any of the following (1) to (3):

(1) 7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-2-pentafluoropropionyl-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(2) 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and

(3) 2-(2-hexynoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

[18] The novel heterocyclic compound of [1] above, wherein the

compound of the formula (I) is any of the following (1) to

(17):

- (1) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (2) 2-(2-heptenoyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (3) 2-(2,4-hexadienoyl)-7-{2-[2-(1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (4) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(5-methyl-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (5) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (6) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (7) 2-(2-hexenoyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (8) 7-{2-[5-methyl-2-(1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(2,2,3,3,3-pentafluoropropionyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (9) 7-{2-[2-(4,4-dimethyl-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (10) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(3-methyl-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (11) 2-(2,4-hexadienoyl)-7-(2-{5-methyl-2-[2-(1-

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- methylocyclohexan-1-yl)vinyl]oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (12) 7-{2-[2-(3,3-dimethyl-1-buten-1-yl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (13) 2-(2,4-hexadienoyl)-7-{2-[2-(3-methoxy-1-propen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (14) 7-{2-[2-(2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (15) 7-{2-[2-(2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (16) 2-(3-butenyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and
- (17) 7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

[19] The novel heterocyclic compound of [1] above, wherein the compound of the formula (I) is any of the following (1) to (8):

- (1) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (2) 2-(2,4-hexadienoyl)-7-[2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (3) 2-(2-heptenoyl)-7-[2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(4) 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(5) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(6) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(7) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and

(8) 2-(2-hexenoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

[20] The novel heterocyclic compound of [1] above, wherein the compound of the formula (I) is any of the following (1) to (6):

(1) 7-{2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(2,2,3,3,3-pentafluoropropionyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(2) 7-{2-[2-(4,4-dimethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(3) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(3-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(4) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-[2-trans-(1-methylcyclohexan-1-yl)vinyl]oxazol-4-yl]ethoxy}-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylic acid,

(5) 7-{2-[2-(3,3-dimethyl-trans-1-buten-1-yl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and

(6) 2-(2,4-hexadienoyl)-7-{2-[2-(3-methoxy-trans-1-propen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

[21] The novel heterocyclic compound of [1] above, wherein the compound of the formula (I) is the following (1) or (2):

(1) 7-{2-[2-(trans-2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(2) 7-{2-[2-(trans-2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

[22] The novel heterocyclic compound of [1] above, wherein the compound of the formula (I) is the following (1) or (2):

(1) 2-(3-butenyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(2) 7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

[23] The novel heterocyclic compound of [1] above, wherein the compound of the formula (I) is any of the following (1) to (9):

(1) 2-(2,4-hexadienoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

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- (2) 7-{2-[2-(trans-2-cyclopentylvinyl)oxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (3) 7-{2-[2-(trans-2-cyclohexylvinyl)oxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (4) 2-(2-heptenoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (5) 2-(2-hexenoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (6) 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (7) 2-(2,4-hexadienoyl)-7-{2-[2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (8) 2-(2,4-hexadienoyl)-7-{2-[2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid and
- (9) 2-(2,4-hexadienoyl)-7-{2-[(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- or a pharmaceutically acceptable salt thereof.
- [24] A pharmaceutical composition containing the novel heterocyclic compound of any of [1] to [23] above, or a pharmaceutically acceptable salt thereof.
- [25] A pharmaceutical agent containing the novel heterocyclic compound of any of [1] to [23] above, or a pharmaceutically acceptable salt thereof, which agent is selected from the group consisting of a hypoglycemic agent, a hypolipidemic agent, an insulin resistance improver, a therapeutic agent of diabetes, a

therapeutic agent of diabetic complications, a glucose

tolerance improver, an anti-arteriosclerosis agent, an anti-

obesity agent, an antiinflammatory agent, an agent for the

prophylaxis or treatment of PPAR-mediated diseases or an agent

for the prophylaxis or treatment of syndrome X.

[26] A method for the prophylaxis or treatment of hyperglycemia,

hyperlipidemia, diseases caused by insulin resistance, diabetes,

diabetic complication, impaired glucose tolerance,

arteriosclerosis, obesity, inflammation, PPAR-mediated disease

or syndrome X, which comprises administering a pharmaceutically

effective amount of the heterocyclic compound of any of [1] to

[23]-above or a pharmaceutically 'acceptable salt thereof to a

patient.

[27] Use of a novel heterocyclic compound of any of [1] to [23]

above or a pharmaceutically acceptable salt thereof for the

production of a pharmaceutical composition for the prophylaxis

or treatment of hyperglycemia, hyperlipidemia, diseases caused

by insulin resistance, diabetes, diabetic complication,

impaired glucose tolerance, arteriosclerosis, obesity,

inflammation, PPAR-mediated disease or syndrome X.

DETAILED DESCRIPTION OF THE INVENTION

Each symbol used in the present specification is

explained in the following.

The C₁₋₄ alkyl for R⁴, R⁷, R⁹, R¹¹ and R¹⁴ is a linear or

branched chain alkyl having 1 to 4 carbon atoms, such as methyl,

ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-

butyl and the like, preferably methyl, ethyl, propyl and

isopropyl.

The C₁₋₆ alkyl for R¹, R¹⁰ and R¹² is a linear or branched

chain alkyl having 1 to 6 carbon atoms, such as methyl, ethyl,

propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl,

pentyl, isopentyl, neopentyl, hexyl and the like, preferably

methyl, ethyl, propyl, tert-butyl, butyl, isobutyl and

isopentyl.

The C₁₋₈ alkyl for R⁵, R⁶ and R¹³ is a linear or branched chain alkyl having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl and the like, preferably methyl, ethyl, propyl, tert-butyl, butyl, pentyl and hexyl.

The C₅₋₈ alkyl for R⁸ is a linear or branched chain alkyl having 5 to 8 carbon atoms, such as pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl and the like, preferably pentyl, neopentyl and hexyl.

In the C₂₋₆ alkyl optionally substituted by halogen for R³, halogen is chlorine atom, bromine atom, iodine atom or fluorine atom. The C₂₋₆ alkyl is a linear or branched chain alkyl having 2 to 6 carbon atoms, such as ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hexyl and the like. The C₂₋₆ alkyl substituted by halogen is exemplified by 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2,2,3,3-tetrafluoropropyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, 6,6,6-trifluorohexyl and the like, preferably 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and 2,2,3,3-tetrafluoropropyl.

In the C₁₋₆ alkyl optionally substituted by halogen for R² and R¹⁰, halogen is chlorine atom, bromine atom, iodine atom or fluorine atom. The C₁₋₆ alkyl is a linear or branched chain alkyl having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hexyl and the like. The C₁₋₆ alkyl substituted by halogen is exemplified by fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 2-chloroethyl, 2-bromoethyl, 2-

iodoethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2,2,3,3-tetrafluoropropyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3,2,2-pentafluoropropyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, 6,6,6-trifluorohexyl and the like, preferably 3-fluoropropyl, 3,3-difluoropropyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 3,3,3-trifluoropropyl and 3,3,3,2,2-pentafluoropropyl.

The C_{3-8} cycloalkyl for R^2 and R^{10} is cycloalkyl having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like, preferably cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The C_{4-8} cycloalkyl for R^8 is cycloalkyl having 4 to 8 carbon atoms, such as, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like, preferably cyclopentyl and cyclohexyl.

The C_{2-8} alkenyl for R^5 and R^{10} is a linear or branched chain alkenyl having 2 to 8 carbon atoms, such as vinyl, 1-propenyl, 2-propenyl, isopropenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl and the like, preferably 1-propenyl, 1-butenyl, 1-pentenyl and 1-hexenyl.

The C_{2-6} alkenyl for R^2 is a linear or branched alkenyl having 2 to 6 carbon atoms, such as vinyl, 1-propenyl, 2-propenyl, isopropenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl and the like, preferably 3-butenyl, 4-

pentenyl and 5-hexenyl.

As the aryl for R^2 , R^3 , R^{10} , R^{12} , R^{13} and R^{15} , phenyl, naphthyl and the like, preferably phenyl, are exemplified.

As the aromatic heterocycle for R^5 , R^{10} and R^{15} , a
 5 monocyclic hetero ring and fused hetero ring having at least one hetero atom selected from the group consisting of oxygen atom, nitrogen atom and sulfur atom are preferable. The fused heterocycle in the present invention is a two ring system, which encompasses one having hetero atoms on both rings.
 10 'Preferable monocyclic' hetero ring is a 5- or 6-membered ring. The hetero ring constituting a preferable fused hetero ring is 5- or 6-membered hetero ring, and the ring without a hetero ring constituting a preferable fused heterocycle is a 5 or 6-membered ring. The aromatic hetero ring is, for example, a
 15 monocyclic hetero ring such as furyl, thienyl, pyridyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridazinyl, pyrimidinyl or pyrazinyl and the like; a fused hetero ring such as indolyl, isoindolyl, indolinyl, isoindolinyl, indazolyl, benzofuranyl,
 20 benzothiophenyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, benzoxazinyl, benzothiazinyl, furo[2,3-b]pyridyl, thieno[2,3-b]pyridyl, naphthyridinyl, imidazopyridyl, oxazolopyridyl, thiazolopyridyl and the like, which are preferably furyl, thienyl, pyridyl, oxazolyl, thiazolyl,
 25 indolyl, indolinyl, benzofuranyl, benzothiophenyl, quinolyl and isoquinolyl.

The C_{3-8} cycloalkyl C_{1-3} alkyl for R^2 and R^{10} is that wherein the cycloalkyl moiety has 3 to 8 carbon atoms and the alkyl moiety is a linear or branched chain alkyl having 1 to 3
 30 carbon atoms, such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, cycloheptylethyl,

cyclooctylethyl, cyclopropylpropyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylpropyl, cycloheptylpropyl, cyclooctylpropyl, 1-methylcyclopentyl-1-yl, 1-methylcyclohexyl-1-yl and the like. Preferred are cyclopropylmethyl, cyclopropylethyl, 1-methylcyclopentyl-1-yl, 1-methylcyclohexyl-1-yl, cyclopentylmethyl and cyclohexylmethyl.

The C_{1-4} alkoxy C_{1-6} alkyl for R^{10} is that wherein the alkoxy moiety is a linear or branched chain alkyl having 1 to 4 carbon atoms and the alkyl moiety is a linear or branched chain alkyl having 1 to 6 carbon atoms, such as methoxymethyl, ethoxymethyl, propyloxymethyl, isopropyloxymethyl, butoxymethyl, methoxyethyl, ethoxyethyl, propyloxyethyl, butoxyethyl, methoxypropyl, ethoxypropyl, propyloxypropyl, butoxypropyl, methoxybutyl, ethoxybutyl, propyloxybutyl, butoxybutyl, methoxypentyl, ethoxypentyl, propyloxypentyl, butoxypentyl, methoxyhexyl, ethoxyhexyl, propyloxyhexyl, butoxyhexyl and the like. Preferred are methoxymethyl, methoxyethyl, ethoxymethyl, propyloxymethyl, isopropyloxymethyl and ethoxyethyl.

The optionally substituted aryl C_{1-3} alkyl for R^2 is aryl substituted by at least one linear or branched chain alkyl having 1 to 3 carbon atoms, such as that wherein the aryl moiety is phenyl, naphthyl and the like and the alkyl moiety is a linear or branched alkyl having 1 to 3 carbon atoms. When it is not substituted by the above-mentioned substituent, it is, for example, benzyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-phenylethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 3-phenylpropyl, 3-(1-naphthyl)propyl, 3-(2-naphthyl)propyl, 1-phenylethyl, 2-phenylpropyl, 1-(1-naphthyl)ethyl, 1-(2-naphthyl)ethyl, 1-(1-naphthyl)propyl, 1-(2-naphthyl)propyl, 2-(1-naphthyl)propyl, 2-(2-naphthyl)propyl and the like. Preferred are benzyl, 2-phenylethyl, 3-phenylpropyl, 1-naphthylmethyl and 2-naphthylmethyl. Examples of the substituent include C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, halogen

atom (e.g., chlorine, bromine, iodine, fluorine), nitro, amino and the like. The number of the substituent is preferably 1 or 2.

The C_{1-4} alkylthio C_{1-6} alkyl for R^8 and R^{10} is that wherein the alkyl moiety of the alkylthio moiety is a linear or branched chain alkyl having 1 to 4 carbon atoms and the alkyl moiety is a linear or branched chain alkyl having 1 to 6 carbon atoms, such as methylthiomethyl, methylthioethyl, methylthiopropyl, methylthiobutyl, methylthiopentyl, methylthiohexyl, ethylthiomethyl, ethylthioethyl, ethylthiopropyl, ethylthiobutyl, ethylthiopentyl, ethylthiohexyl, propylthiomethyl, propylthioethyl, propylthiopropyl, propylthiobutyl, propylthiopentyl, propylthiohexyl, isopropylthiomethyl, butylthiomethyl, butylthioethyl, butylthiopropyl, butylthiobutyl, butylthiopentyl, butylthiohexyl and the like. Preferred are methylthiomethyl, methylthioethyl, ethylthiomethyl, ethylthioethyl, isopropylthiomethyl and methylthiopropyl.

The C_{1-6} alkyl substituted by $(R^9)_2N-$, wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl, for R^{10} is that wherein the alkyl moiety, which is alkyl having 1 to 6 carbon atoms, is substituted by the aforementioned $(R^9)_2N-$. Examples of such C_{1-6} alkyl substituted by $(R^9)_2N-$ include aminomethyl, methylaminomethyl, dimethylaminomethyl, aminoethyl, methylaminoethyl, dimethylaminoethyl, aminopropyl, dimethylaminopropyl, aminobutyl, aminopentyl, aminoethyl, diethylaminomethyl, diethylaminoethyl, ethylaminoethyl and the like. Preferred are aminomethyl, methylaminomethyl, dimethylaminomethyl, aminoethyl, methylaminoethyl, dimethylaminoethyl, aminopropyl and dimethylaminopropyl.

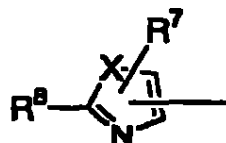
R^1 is preferably a hydrogen atom.

Preferable R^2 is $-CO-C(R^4)=C(R^4)-R^5$ wherein R^4 is a

hydrogen atom and R^5 is C_{1-8} alkyl or C_{2-8} alkenyl, or $-CO-C\equiv C-R^6$ wherein R^6 is C_{1-8} alkyl, or C_{2-8} alkenyl.

In the formula (I), $Y-(CH_2)_n-O-$ is preferably bonded to the 7-position of the tetrahydroisoquinoline skeleton. In $Y-(CH_2)_n-O-$, n is preferably 2.

Y is preferably a group of the formula



wherein each symbol is as defined above.

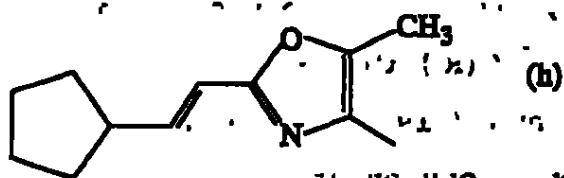
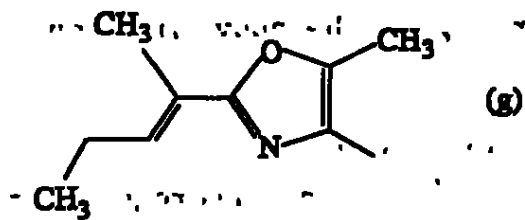
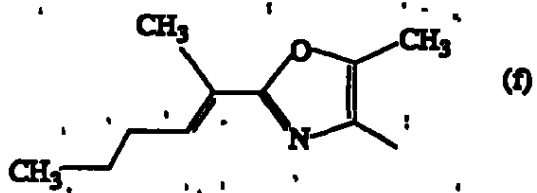
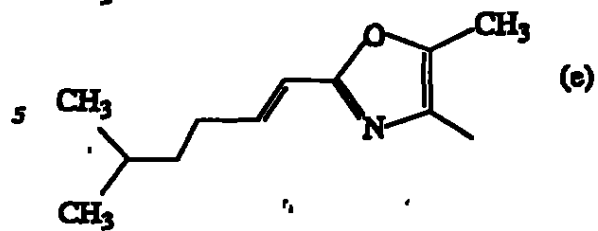
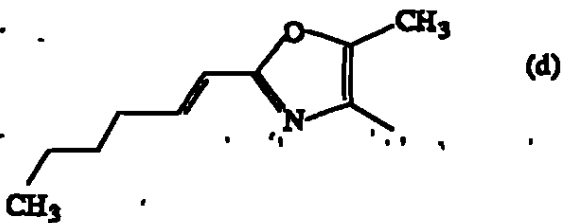
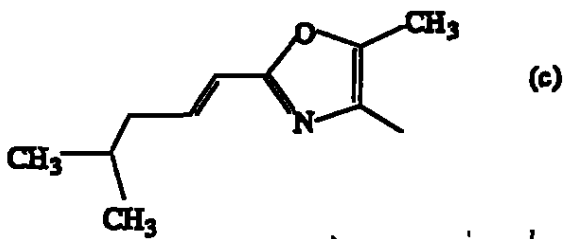
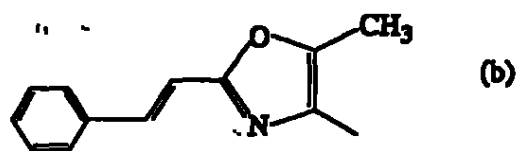
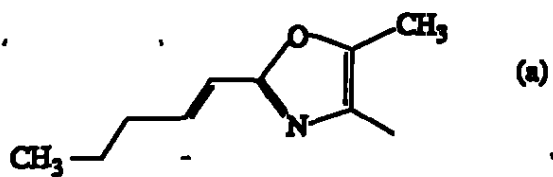
More preferable Y is that wherein, in the above-mentioned formula,

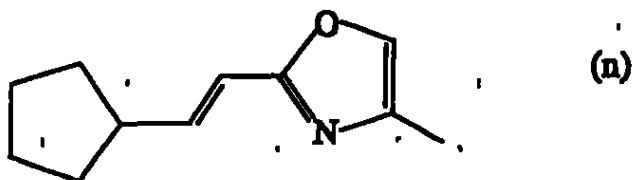
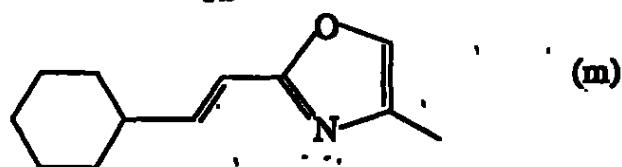
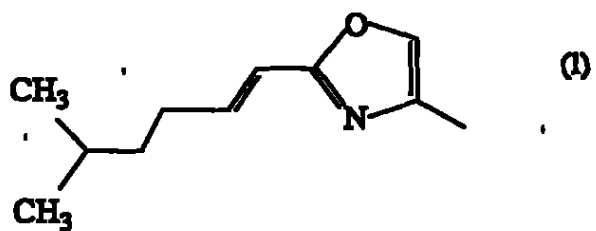
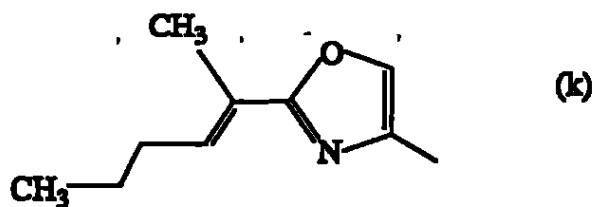
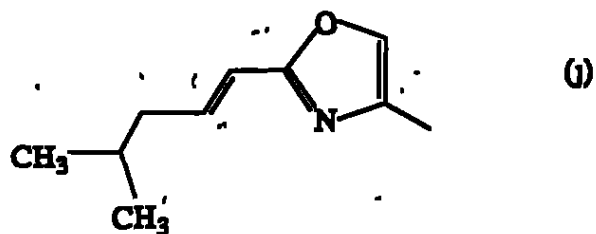
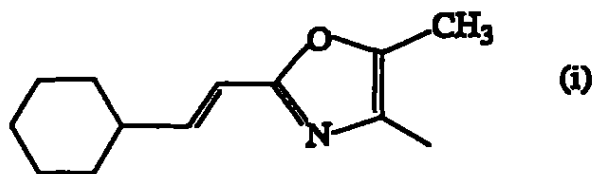
- (1) R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl and R^{10} is C_{1-8} alkyl, C_{2-8} alkenyl or aryl,
 - (2) R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is $R^{13}-Z-$ wherein R^{13} is C_{1-8} alkyl or aryl and Z is a sulfur atom,
 - (3) R^7 is a hydrogen atom or C_{1-4} alkyl and R^8 is C_{3-8} alkyl or C_{4-8} cycloalkyl,
 - (4) R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is a hydrogen atom and R^{10} is C_{3-8} cycloalkyl, and
- more preferable Y is that wherein, in the above-mentioned formula,
- (5) R^7 is C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl, R^{10} is C_{1-8} alkyl, and X is an oxygen atom, or
 - (6) R^7 is C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is a hydrogen atom, R^{10} is aryl, and X is an oxygen atom.

X for Y is preferably an oxygen atom.

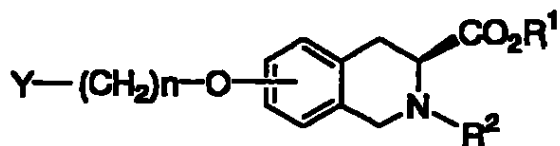
Particularly preferable Y is selected from the following (a) to (n).

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46





The heterocyclic compound (I) comprises stereoisomers due to an asymmetric carbon at the 3-position carbon of 1,2,3,4-tetrahydroisoquinoline ring. The most preferable configuration is



wherein R^1 , R^2 , Y and n are as defined above.

When, in the formula (I), R^2 is $-\text{CO}-\text{C}(R^4)=\text{C}(R^4)-R^5$ wherein R^4 and R^5 are as defined above, R^3 is $R^{10}-\text{C}(R^9)=\text{C}(R^9)-$ wherein R^9 and R^{10} are as defined above, or Y is $R^{15}-\text{C}(R^{14})=\text{N}-\text{O}-$ wherein R^{14} and R^{15} are as defined above, stereoisomers (Z form and E form) are present at the double bond or the oxime moiety, both isomers of which are encompassed in the present invention.

The compound (I) of the present invention may form a pharmaceutically acceptable salt.

When the compound (I) has a basic group, an acid addition salt can be formed. The acid for forming such acid addition salt is not particularly limited, as long as it can form a salt with a basic part and is a pharmaceutically acceptable acid.

Examples of the acid include inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid and the like, and organic acids such as oxalic acid, fumaric acid, maleic acid, citric acid, tartaric acid, methanesulfonic acid, toluenesulfonic acid and the like.

When the compound (I) has an acidic group such as carboxyl group and the like, for example, alkali metal salts (e.g., sodium salt, potassium salt and the like), alkaline earth metal salts (e.g., calcium salt, magnesium salt and the like), organic base salts (e.g., tert-butylamine salt, triethylamine salt, dicyclohexylamine salt, ethanolamine salt, pyridine salt, and the like) and the like can be formed.

Examples of the heterocyclic compound of the formula (I) and a pharmaceutically acceptable salt thereof include the following:

(1) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-styryloxazol-4-

- yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (2) 2-(2-heptenoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-
 1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (3) 2-(2-hexynoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-
 5 1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (4) 7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-2-
 pentafluoropropionyl-1,2,3,4-tetrahydroisoquinoline-(3S)-
 11 carboxylic acid,
 (5) 2-(2-heptenoyl)-7-[2-(5-methyl-2-styrylthiazol-4-
 10 yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (6) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-
 4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic
 15 acid,
 (7) 2-(2-heptenoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-
 yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (8) 2-(2-hexynoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-
 yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (9) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(1,3-pentadien-1-
 20 yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-
 carboxylic acid,
 (10) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-pentyloxazol-4-
 yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (11) 7-[2-(2-cyclopentyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-
 hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic
 25 acid,
 (12) 7-[2-(2-cyclohexyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-
 hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic
 acid,
 (13) 7-[2-(2-benzoylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-
 30 1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (14) 7-[2-(2-butyrylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-
 1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (15) 2-(2-heptenoyl)-7-[2-(4-methyl-2-phenylsulfanythiazol-5-

yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

and

(16) 2-(2-heptenoyl)-7-[2-(1-phenylethylideneaminoxy)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and

5 pharmaceutically acceptable salts thereof

Of the aforementioned examples (1)-(16), the following compounds (1)-(3) and pharmaceutically acceptable salts thereof are particularly preferable, because they have a superior hypoglycemic action, a blood hypolipidemic action, an insulin
10 resistance-improving action and a PPAR (peroxisome proliferator-activated receptor) activating action:

(1) 7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-2-pentafluoropropionyl-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

15 (2) 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and

(3) 2-(2-hexynoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-
20 carboxylic acid.

The following compounds (1)-(17) and pharmaceutically acceptable salts thereof are preferable examples of the present invention.

(1) 2-(2,4-hexadienoyl)-7-[2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-
25 carboxylic acid,

(2) 2-(2-heptenoyl)-7-[2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

30 (3) 2-(2,4-hexadienoyl)-7-[2-[2-(1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(4) 2-(2,4-hexadienoyl)-7-[2-[5-methyl-2-(5-methyl-1-hexen-1-

- yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (5) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-1-penten-1-
yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
5 carboxylic acid,
- (6) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-1-buten-1-
yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (7) 2-(2-hexenoyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-
10 yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (8) 7-{2-[5-methyl-2-(1-penten-1-yl)oxazol-4-yl]ethoxy}-2-
(2,2,3,3,3-pentafluoropropionyl)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylic acid,
- 15 (9) 7-{2-[2-(4,4-dimethyl-1-penten-1-yl)-5-methyloxazol-4-
yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid,
- (10) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(3-methyl-1-buten-1-
yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
20 carboxylic acid,
- (11) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-[2-(1-
methylcyclohexan-1-yl)vinyl]oxazol-4-yl]ethoxy}-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylic acid,
- (12) 7-{2-[2-(3,3-dimethyl-1-buten-1-yl)-5-methyloxazol-4-
25 yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid,
- (13) 2-(2,4-hexadienoyl)-7-{2-[2-(3-methoxy-1-propen-1-yl)-5-
methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- 30 (14) 7-{2-[2-(2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy}-
2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (15) 7-{2-[2-(2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-

- (2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (16) 2-(3-butenyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and
 (17) 7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid.

In addition, the following compounds (1)-(8), and pharmaceutically acceptable salts thereof are preferable examples of the present invention:

- (1) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (2) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (3) 2-(2-heptenoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (4) 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (5) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (6) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
 (7) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and
 (8) 2-(2-hexenoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-

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-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid.

Furthermore, the following compounds (1)-(6), and
pharmaceutically acceptable salts thereof are preferable
examples of the present invention:

- (1) 7-{2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-
2-(2,2,3,3,3-pentafluoropropionyl)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylic acid,
(2) 7-{2-[2-(4,4-dimethyl-trans-1-penten-1-yl)-5-methyloxazol-
4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylic acid,
(3) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(3-methyl-trans-1-
buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid,
(4) 2-(2,4-hexadienoyl)-7-(2-{5-methyl-2-[2-trans-(1-
methylcyclohexan-1-yl)vinyl]oxazol-4-yl}ethoxy)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylic acid,
(5) 7-{2-[2-(3,3-dimethyl-trans-1-buten-1-yl)-5-methyloxazol-4-
yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid, and
(6) 2-(2,4-hexadienoyl)-7-{2-[2-(3-methoxy-trans-1-propen-1-
yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid.

Moreover, the following compounds (1) and (2), and
pharmaceutically acceptable salts thereof are preferable
examples of the present invention:

- (1) 7-{2-[2-(trans-2-cyclopentylvinyl)-5-methyloxazol-4-
yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid, and
(2) 7-{2-[2-(trans-2-cyclohexylvinyl)-5-methyloxazol-4-
yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid.

Additionally, the following compounds (1) and (2), and

pharmaceutically acceptable salts thereof are preferable examples of the present invention:

- (1) 2-(3-butenyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and
- (2) 7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid.

Furthermore, the following compounds (1)-(9), and pharmaceutically acceptable salts thereof are preferable examples of the present invention:

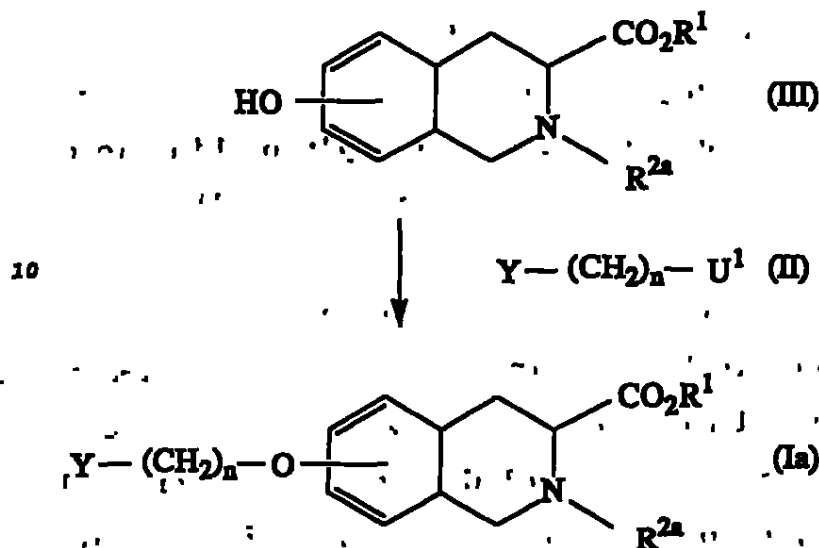
- (1) 2-(2,4-hexadienoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (2) 7-{2-[2-(trans-2-cyclopentylvinyl)oxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (3) 7-{2-[2-(trans-2-cyclohexylvinyl)oxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (4) 2-(2-heptenoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (5) 2-(2-hexenoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (6) 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (7) 2-(2,4-hexadienoyl)-7-{2-[2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (8) 2-(2,4-hexadienoyl)-7-{2-[2-(1-methyl-trans-1-buten-1-

yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid, and

(9) 2-(2,4-hexadienoyl)-7-{2-[(5-methyl-trans-1-hexen-1-
yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-
5 carboxylic acid.

The compound (I) of the present invention and a
pharmaceutically acceptable salt thereof can be produced by any
of the following production methods.

Production Method 1



wherein R^1 , Y and n are as defined above, R^{2a} is $-CO-R^3$ wherein
 R^3 is as defined above, $-CO-C(R^4)=C(R^4)-R^5$ wherein R^4 and R^5 are
as defined above, $-CO-C\equiv C-R^6$ wherein R^6 is as defined above,
aryl, optionally substituted aryl, C_{1-3} alkyl, C_{1-6} alkyl
15 optionally substituted by halogen, C_{2-6} alkenyl, C_{3-8} cycloalkyl
or C_{3-8} cycloalkyl, C_{1-3} alkyl, and U^1 is hydroxy and/or a leaving
group such as halogen atom (fluorine atom, chlorine atom,
bromine atom, iodine atom) or, alkane sulfonyloxy (e.g.,
methane sulfonyloxy, ethane sulfonyloxy, propane sulfonyloxy,
20 trifluoromethane sulfonyloxy and the like), aryl sulfonyloxy
(e.g., phenyl sulfonyloxy and tolyl sulfonyloxy and the like).

In Production Method 1, a compound having the formula
(II) (compound (II)) is reacted with a compound having the
formula (III) (compound (III)) to produce a compound having the

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formula (Ia) (compound (Ia)).

Production Method 1-a: When U¹ is hydroxy group, Production Method 1 includes a dehydrating reaction such as Mitsunobu reaction (Reagents for Organic Synthesis by Fieser & Fieser, Vol. 6,645) and the like. The reaction generally proceeds in the presence of a solvent using an azo compound and a phosphine. Examples of the azo compound include di-C₁₋₄ alkyl azodicarboxylate (e.g., dimethyl azodicarboxylate, diethyl azodicarboxylate, diisopropyl azodicarboxylate and the like), azodicarboxamide (e.g., 1,1'-azobis(N,N'-dimethylformamide), 1,1'-(azodicarbonyl)dipiperidine and the like) and the like. Examples of the phosphine include triarylphosphine (e.g., triphenylphosphine and the like), tri(C₁₋₈ alkyl)phosphine (e.g., tri-n-butylphosphine, tri-n-hexylphosphine, tri-n-octylphosphine and the like) and the like.

The solvent to be used in Production Method 1-a is free of any particular limitation as long as it is inert to the reaction. Examples thereof include dioxane, acetonitrile, tetrahydrofuran, chloroform, methylene chloride, ethylene chloride, benzene, toluene, xylene, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide and the like, a mixture of these, and the like.

The amount of compound (II) to be used in Production Method 1-a is free of any particular limitation, and is generally 1-5 moles; preferably 1-3 moles, per 1 mole of compound (III). The amount of the azo compound and the phosphine to be used is generally 1-3 moles, preferably 1-1.5 moles, per 1 mole of compound (III).

While the reaction conditions in Production Method 1-a, such as reaction temperature, reaction time and the like vary depending on the reaction reagent, reaction solvent and the like to be used, the reaction is generally carried out at -30°C to 50°C for 30 min to about a dozen hours.

Production Method 1-b: When U^1 is a leaving group such as halogen atom or, alkanesulfonyloxy, (e.g., methanesulfonyloxy, ethanesulfonyloxy, propanesulfonyloxy, trifluoromethanesulfonyloxy and the like), arylsulfonyloxy (e.g., phenylsulfonyloxy, tolylsulfonyloxy and the like) and the like, Production Method 1-b is performed in a solvent similar to those used in Production Method 1-a in the presence of a base

The base to be used in Production Method 1-b is free of any particular limitation, and is exemplified by inorganic bases such as alkali metal carbonates (e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium bicarbonate and the like), alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide and the like), metal hydride compounds (e.g., sodium hydride, potassium hydride, calcium hydride and the like) and the like; and organic bases such as alkali metal alcoholates (e.g., sodium methoxide, sodium ethoxide, potassium-t-butoxide and the like), amines (e.g., triethylamine, diisopropylethylamine and the like) and the like.

The amount of compound (II) to be used in Production Method 1-b is free of any particular limitation, and is generally 1-5 moles, preferably 1-3 moles, per 1 mole of compound (III). The amount of the base to be used is generally 1-5 moles, preferably 1-3 moles, per 1 mole of compound (III).

In Production Method 1-b, a catalyst can be used in a solvent in the presence of a base. Preferable solvent is toluene and the catalyst is exemplified by quaternary ammonium salts such as tetramethyl ammonium bromide, tetraethyl ammonium bromide, tetrabutyl ammonium bromide, tetraethyl ammonium chloride, tetraethyl ammonium fluoride, benzyltrimethyl ammonium bromide and the like, and tris[2-(2-methoxyethoxy)ethyl]amine. Preferably, tetraethylammonium

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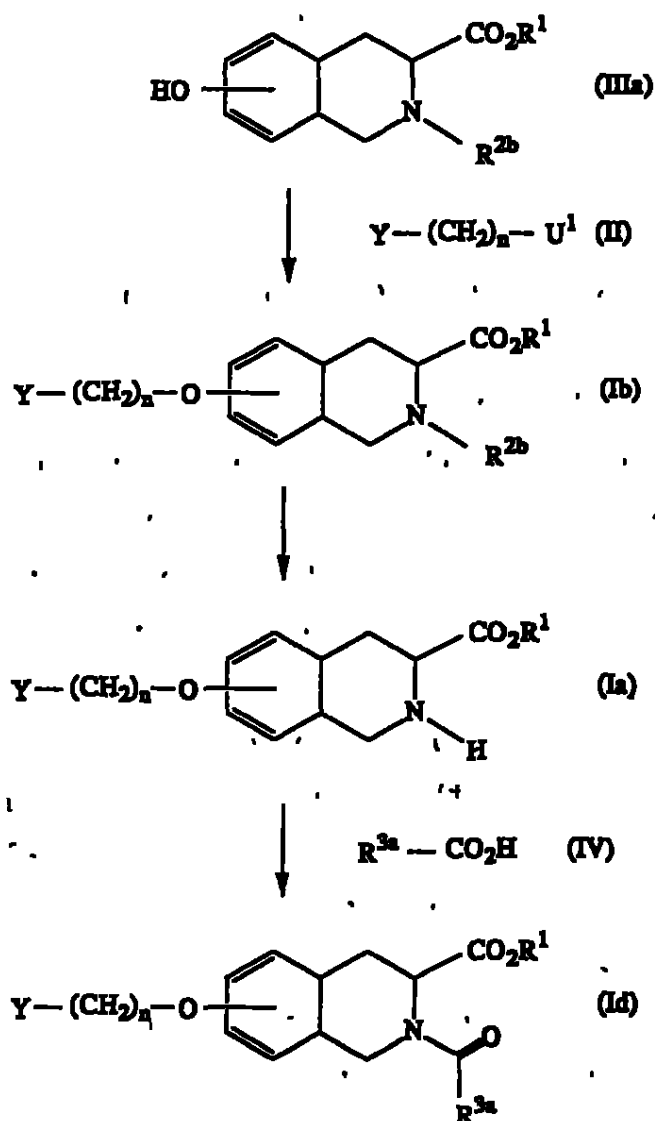
fluoride or tris[2-(2-methoxyethoxy)ethyl]amine is used. The

amount of catalyst to be used is generally 0.1-1 mole, preferably 0.1-0.5 mole, per 1 mole of compound (III).

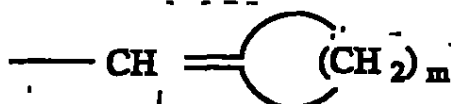
While the reaction conditions in Production Method 1-b, such as reaction temperature, reaction time and the like vary depending on the reaction reagent, reaction solvent and the like to be used, the reaction is generally carried out at -30°C to 150°C for 30 min to about a dozen hours.

In Production Method 1-a and Production Method 1-b, R¹ of compound (III) is preferably a C₁₋₆ alkyl group. In this case, a compound (Ia) wherein R¹ is a C₁₋₆ alkyl group is obtained, which is hydrolyzed by a method known per se to give a compound (Ia) wherein R¹ is a hydrogen atom.

Production Method 2



wherein R^1 , Y, n and U^1 are as defined above, R^{2b} is an amino-protecting group, and R^{3a} is C_{2-6} alkyl optionally substituted by halogen, $-\text{C}(\text{R}^4)=\text{C}(\text{R}^4)-\text{R}^5$ wherein R^4 and R^5 are as defined above, $-\text{C}_m\text{C}-\text{R}^6$ wherein R^6 is as defined above or



wherein m is an integer of 2 to 7.

The amino-protecting group for R^{2a} is exemplified by formyl, monochloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, diphenylmethyloxycarbonyl; methoxymethylcarbonyl;

methoxymethyloxycarbonyl, trimethylsilyl, 2,2,2-trichloroethoxycarbonyl, 2-methylsulfonylethyloxycarbonyl, tert-butoxycarbonyl (hereinafter to be also referred to as Boc), trityl and the like.

5 In Production Method 2, the amino-protecting group of a compound having the formula (Ib) (compound (Ib)) is removed by a method known per se to give a compound having the formula (Ic) (compound (Ic)), which is reacted with a compound having the formula (IV) (compound (IV)) to give a compound having the
10 formula (Id) (compound (Id)). The compound (Ib) can be produced by reacting compound (II) and a compound having the formula (IIIa) (compound (IIIa)) in the reaction mode and reaction conditions similar to those of the reaction between compound (II) and compound (III) in Production Method 1.

15 In Production Method 2, the compound (IV) is subjected to the reaction not only in the form of a free acid but also in the form of a salt (e.g., salt of sodium, potassium, calcium, triethylamine, pyridine and the like), a reactive derivative (e.g., acid halide such as acid chloride, acid bromide and the
20 like; acid anhydride; mixed acid anhydride with substituted phosphoric acid (e.g., dialkylphosphoric acid and the like), with alkylcarbonate (e.g., monoethyl carbonate and the like), and the like; active amide which is an amide with imidazole and
the like; esters such as cyanomethyl ester, 4-nitrophenyl ester
25 and the like; and the like.

When compound (IV) is used in the form of a free acid or a salt in Production Method 2, the reaction is preferably carried out in the presence of a condensing agent. Examples of the condensing agent include dehydrating agents such as
30 carbodiimide compounds (e.g., N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide and the like); azolide

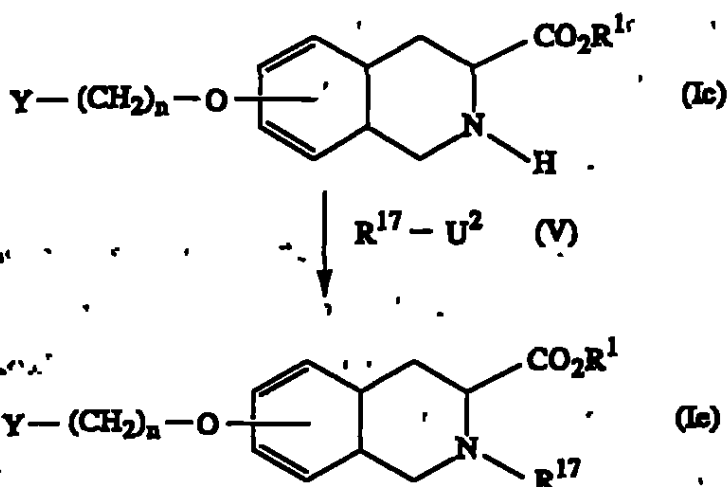
compounds (e.g., N,N'-carbonyldiimidazole, N,N'-thionyl-diimidazole and the like) and the like; and the like. When these condensing agents are used, the reaction is considered to proceed via a reactive derivative of compound
5 (IV).

In Production Method 2, the reaction between compound (Ic) and compound (IV) is generally carried out in an inert solvent. Examples of the solvent include acetone, dioxane, acetonitrile, chloroform, benzene, methylene chloride, ethylene
10 chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine, water and the like, mixtures of these and the like. In addition, a base such as triethylamine, pyridine, 4-dimethylaminopyridine, potassium carbonate and the like can be used. When such base is used, the amount of the base to be
15 used is generally 1-5 moles, preferably 1-3 moles, per 1 mole of compound (Ic).

In Production Method 2, the amount of compound (IV) to be used is generally 1-5 moles, preferably 1-3 moles, per 1 mole of compound (Ic).

20 While the reaction conditions of compound (Ic) and compound (IV) in Production Method 2, such as reaction temperature, reaction time and the like vary depending on the reaction reagent, reaction solvent and the like to be used, the reaction is generally carried out at -30°C to 150°C for 30 min
25 to about a dozen hours.

Production Method 3



wherein R^1 , Y and n are as defined above, R^{17} is C_1-8 alkyl optionally substituted by halogen, C_3-8 cycloalkyl, C_3-8 cycloalkyl C_1-3 alkyl or optionally substituted aryl C_1-3 alkyl, and U^2 is a leaving group such as a halogen atom, alkanesulfonyloxy group (e.g., methanesulfonyloxy, ethanesulfonyloxy, propanesulfonyloxy, trifluoromethanesulfonyloxy and the like), arylsulfonyloxy group (e.g., phenylsulfonyloxy and tolylsulfonyloxy and the like), and the like.

In Production Method 3, compound (Ic) is reacted with a compound having the formula (V) (compound (V)) to give a compound having the formula (Ie) (compound (Ie)).

The reaction between compound (Ic) and compound (V) to form compound (Ie) can be carried out in a solvent inert to the reaction in the presence of a base. Examples of the solvent include dioxane, acetonitrile, tetrahydrofuran, chloroform, methylene chloride, ethylene chloride, benzene, toluene, xylene, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide and the like, mixtures of these and the like.

The ratio of the molar amounts of compound (Ic) and compound (V) to be used is free of any particular limitation, but 1-5 moles, preferably 1-3 moles, of compound (V) is used, per 1 mole of compound (Ic).

The base to be used in this reaction is free of any particular limitation, and is exemplified by inorganic bases such as alkali metal carbonates (e.g., sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate and the like), alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide and the like) and the like; alkali metal alcoholates such as sodium methoxide, sodium ethoxide, potassium-t-butoxide and the like; metal hydride compounds such as sodium hydride, potassium hydride, calcium hydride and the like; and organic bases such as triethylamine, diisopropylethylamine and the like.

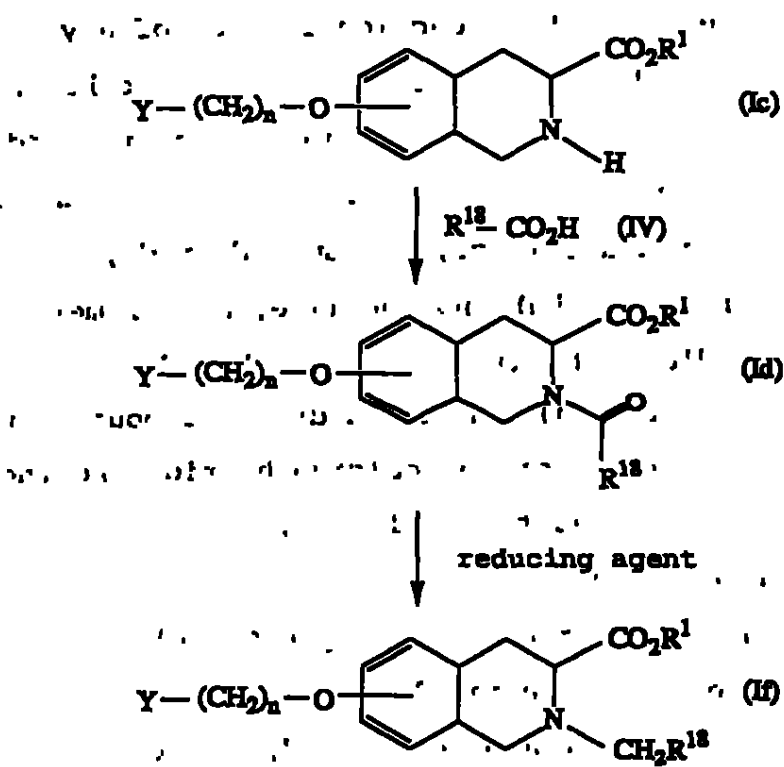
The ratio of the molar amounts of compound (Ic) and the base to be used is free of any particular limitation, but 1-5 moles, preferably 1-3 moles, of a base is used, per 1 mole of compound (Ic).

While the reaction conditions, such as reaction temperature, reaction time and the like vary depending on the reaction reagent, reaction solvent and the like to be used, the reaction is generally carried out at -30°C to 150°C for 30 min to about a dozen hours.

In this production method, R^1 of compound (Ic) is preferably alkyl group, whereby compound (Ie) wherein R^1 is alkyl group is obtained, which is hydrolyzed by a method known per se to give compound (Ie) wherein R^1 is a hydrogen atom.

25 Production Method 4

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wherein R^1 , Y and n are as defined above, and R^{18} is a group that makes a group of the formula: $-\text{CH}_2\text{R}^{18}$ represent C_{1-6} alkyl optionally substituted by halogen, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl or optionally substituted aryl C_{1-3} alkyl.

In Production Method 4, compound (Id) obtained by reacting compound (Ic) with compound (IV) is reduced with a suitable reducing agent to produce compound (If).

The C_{1-6} "alkyl" optionally substituted by halogen, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl and optionally substituted aryl C_{1-3} alkyl with regard to R^{18} are as defined with regard to R^2 .

In Production Method 4, the reaction between compound (Ic) and compound (IV) to give compound (Id) can be carried out in the same reaction mode and reaction conditions as those of compound (Ic) and compound (IV) in Production Method 2.

In Production Method 4, the solvent to be used for the reaction between compound (Id) and reducing agent to give compound (If) is free of any particular limitation as long as it does not adversely affect the reaction, and is exemplified

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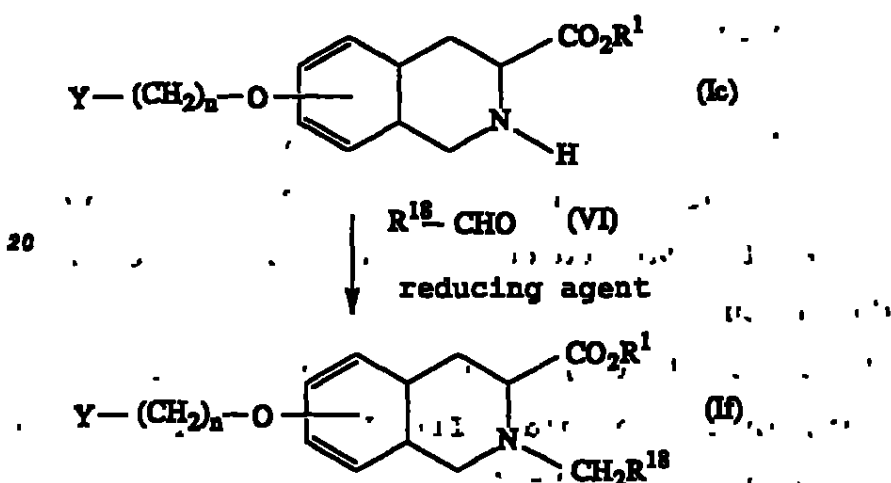
by water, methanol, ethanol, dioxane, acetonitrile, tetrahydrofuran, chloroform, methylene chloride, ethylene chloride, benzene, toluene, xylene, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide and the like, mixtures of these and the like.

The reducing agent to be used for this reaction is not particularly limited and metal hydride complex such as lithium aluminum hydride, sodium cyanoborohydride, sodium borohydride and the like or borane can be used.

The ratio of the molar amounts of compound (Id) and the reducing agent to be used is free of any particular limitation, but 1-5 moles, preferably 1-3 moles, of reducing agent is used per 1 mole of compound (Id).

While the reaction conditions, such as reaction temperature, reaction time and the like vary depending on the reaction reagent, reaction solvent and the like to be used, the reaction is generally carried out at -30°C to 50°C for 30 min to about a dozen hours.

Production Method 5



wherein R^1 , Y, n and R^{18} are as defined above.

In production method 5, compound (Ic) is reacted with compound (VI) in the presence of a suitable reducing agent to produce compound (If).

25 In Production Method 5, the reaction between compound

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(Ic) and compound (VI) to give compound (If) is carried out by condensation in a solvent that does not adversely affect the reaction, such as water, methanol, ethanol, dioxane, acetonitrile, tetrahydrofuran, chloroform, methylene chloride, ethylene chloride, benzene, toluene, xylene, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide and the like, mixtures of these and the like, in the presence of a suitable reducing agent.

The reducing agent to be used for this reaction is not particularly limited and metal hydride complex such as lithium aluminum hydride, sodium cyanoborohydride, sodium borohydride and the like or borane can be used.

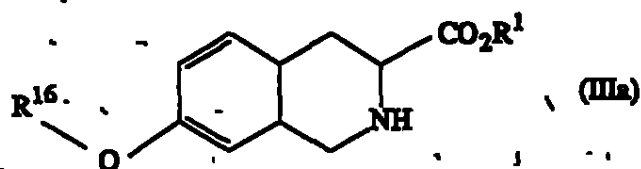
The ratio of the molar amounts of compound (Ic) and compound (VI) to be used is free of any particular limitation, but 1-5 moles, preferably 1-3 moles, of compound (VI) is used per 1 mole of compound (Ic).

The ratio of the molar amounts of compound (Ic) and the reducing agent to be used is free of any particular limitation, but 1-5 moles, preferably 1-3 moles, of reducing agent is used per 1 mole of compound (Ic).

While the reaction conditions, such as reaction temperature, reaction time and the like vary depending on the reaction reagent, reaction solvent and the like to be used, the reaction is generally carried out at -30°C to 50°C for 30 min to about a dozen hours.

When the compound (III) to be used in Production Method 1 is that wherein, in the formula (III), R^{2a} is $-CO-R^3$ wherein R^3 is as defined above, $-CO-C(R^4)=C(R^4)-R^5$ wherein R^4 and R^5 are as defined above, $-CO-C\equiv C-R^6$ wherein R^6 is as defined above, C_{1-6} alkyl optionally substituted by halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-3} alkyl or optionally substituted aryl C_{1-3} alkyl, the reactions of Production Method I can be carried out in the same reaction mode and reaction conditions as those of the

reaction between compound (Ic) and compound (IV) in Production Method 2 or the reaction between compound (Ic) and compound (V) in Production Method 3, or the reaction to obtain compound (If) from compound (Ic) in Production Method 4, using a compound of the formula (IIIa)



wherein R^1 is as defined above and R^{16} is a hydrogen atom or a hydroxy-protecting group, (compound (IIIa)) as a starting material.

When, in the formula (III), R^{2a} is an amino-protecting group, the amino-protecting group can be introduced by a method known *per se*, whereby a compound (III), wherein R^{2a} is an amino-protecting group, can be produced.

Examples of the hydroxy-protecting group to be used for this production method include ethers and acetals such as methyl ether, isopropyl ether, *tert*-butyl ether, benzyl ether, allyl ether, methoxymethyl ether, tetrahydropyranyl ether, *p*-bromophenacyl ether, trimethylsilyl ether and the like, and esters such as formyl, acetyl, monochloroacetyl, dichloroacetyl, trifluoroacetyl, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzoyl, methanesulfonyl, benzenesulfonyl, *p*-toluenesulfonyl and the like.

For production of compound (III), R^{16} of compound (IIIa) is preferably a hydroxy-protecting group. The hydroxy-protecting group can be removed by a method known *per se* to give compound (III) easily.

The heterocyclic compound (I) obtained in the above-mentioned Production Methods 1-5 may be isolated by a conventional method, and optionally purified by a conventional method such as recrystallization, preparative thin-layer

chromatography, column chromatography and the like.

The heterocyclic compound (I) may be converted to a pharmaceutically acceptable salt thereof by a method known per se.

5 A pharmaceutical composition comprising the heterocyclic compound (I) or a pharmaceutically acceptable salt thereof of the present invention may contain an additive and the like. As an additive, exemplified are excipient (e.g., starch, lactose, sugar, calcium carbonate, calcium phosphate and the like),
10 binder (e.g., starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, crystalline cellulose and the like), lubricant (e.g., magnesium stearate, talc and the like), disintegrator (e.g., carboxymethylcellulose calcium, talc and the like), and the like.

15 The above-mentioned components are mixed to give a preparation for oral administration, such as capsule, tablet, powder, granule, dry syrup and the like, or a preparation for parenteral administration, such as injection, suppository and the like, according to a method known per se.

20 While the dose of the heterocyclic compound (I) or a pharmaceutically acceptable salt thereof may vary according to the administration subject, symptom and other factors, when it is orally administered to an adult patient with, for example, diabetes, diabetic complication or hyperlipidemia, the single
25 dose is approximately 1 - 500 mg, which is administered 1 to 3 times a day.

✓ The heterocyclic compound (I) and a pharmaceutically acceptable salt thereof of the present invention show a superior hypoglycemic action, a blood hypolipidemic action, an
30 insulin resistance-improving action and a PPAR activating action in mammals (e.g., human, horse, cattle, dog, cat, rat, mouse, hamster and the like), and are useful as a hypoglycemic agent, a hypolipidemic agent, an insulin resistance improver, a

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therapeutic agent of diabetes, a therapeutic agent of diabetic complication, a glucose tolerance improver, an anti-arteriosclerosis agent, an anti-obesity agent, an antiinflammatory agent, an agent for the prophylaxis or treatment of PPAR-mediated disease or an agent for the prophylaxis or treatment of syndrome X. To be specific, the heterocyclic compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for the prophylaxis or treatment of diabetes, diabetic complication, hyperlipidemia, arteriosclerosis, hyperglycemia, diseases caused by insulin resistance glucose intolerance, diseases caused by insulin resistance, obesity, inflammation, PPAR-mediated disease or syndrome X.

The present invention is explained in more detail by Examples and Reference Examples, which are not to be construed as limitative.

Examples

Example 1

sodium 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

(1) Methyl 2-(2-heptenoyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (500 mg) and 2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethyl methanesulfonate (650 mg) were dissolved in toluene (15 ml), and potassium carbonate (650 mg) and tetraethylammonium fluoride hydrate (100 mg) were added. The mixture was stirred at 80°C for 10 h. To the reaction mixture was added ethyl acetate (50 ml), and the mixture was washed with water (30 ml) and saturated brine (30 ml), and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-

yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (620 mg).

¹H-NMR (CDCl₃) δ (ppm); 0.95 (6H, br-t), 1.15-1.75 (6H, m), 2.00-2.45 (4H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.8Hz), 3.00-3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J=6.8Hz), 4.50-5.70 (3H, m), 6.18 (1H, d, J=15.8Hz), 6.35-7.20 (5H, m), 7.04 (1H, d, J=8.2Hz).

(2) The compound (200 mg) obtained in the above-mentioned (1) was dissolved in a mixture (5 ml) of tetrahydrofuran-methanol (3:1), and 1M aqueous lithium hydroxide solution (1.2 ml) was added. The mixture was stirred at 50°C for 30 min and acidified with 10% aqueous citric acid solution. The solution was concentrated under reduced pressure and the precipitated gummy material was extracted with ethyl acetate (20 ml). The ethyl acetate layer was washed with saturated brine (10 ml) and dried (Na₂SO₄). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-

20 tetrahydroisoquinoline-(3S)-carboxylic acid (170 mg). This was dissolved in methanol (2 ml) and 0.586M sodium hydroxide - methanol solution (0.62 ml) was added; and methanol was evaporated under reduced pressure. The obtained residue was dissolved in water (1 ml) and freeze-dried to give the title compound (170 mg).

IR (KBr) cm⁻¹; 1653, 1595, 1506.

¹H-NMR (DMSO-d₆) δ (ppm); 0.89 (6H, br-t), 1.10-1.75 (6H, m), 1.90-2.20 (4H, m), 2.25 (3H, s), 2.79 (2H, br-t), 3.00-3.30 (2H, br), 4.07 (2H, br-t), 4.20-5.15 (3H, m), 6.19 (1H, d, J=16.7Hz), 6.30-6.80 (5H, m), 6.96 (1H, d, J=8.4Hz).

Example 2

2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-

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carboxylic acid

(1) Methyl 2-tert-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (0.5 g) and 2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethyl

methanesulfonate (0.67 g) were dissolved in toluene (5 ml), and potassium carbonate (0.68 g) and tetraethylammonium fluoride hydrate (0.12 g) were added. The mixture was stirred at 80°C for 18 h. To the reaction mixture was added ethyl acetate (20 ml), and the mixture was washed with water (20 ml) and

saturated brine (20 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 2-tert-butoxycarbonyl-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (0.57 g).

IR ν (neat) cm^{-1} : 1746, 1698, 1615, 1533, 1505.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.89 (3H, t, $J=7.0\text{Hz}$), 1.20-1.80 (11H, m), 2.00-2.40 (2H, m), 2.28 (3H, s), 2.89 (2H, t, $J=6.8\text{Hz}$), 2.90-3.20 (2H, m), 3.61 (3H, s), 4.15 (2H, t, $J=6.8\text{Hz}$), 4.40-4.90 (2H, m), 5.00-5.20 (1H, m), 6.18 (1H, d, $J=16.1\text{Hz}$), 6.73 (1H, dt, $J=16.1, 6.8\text{Hz}$), 6.50-6.80 (2H, m), 7.01 (1H, d, $J=8.4\text{Hz}$).

(2) The compound (0.55 g), obtained in the above-mentioned (1) was dissolved in formic acid (3 ml), and 8.78M hydrogen chloride - 2-propanol solution (0.39 ml) was added under ice-cooling. The mixture was stirred at room temperature for 30 min and ethyl acetate (20 ml) was added to the reaction mixture. After neutralization with saturated aqueous sodium hydrogen carbonate, two layers were separated and the obtained ethyl acetate layer was washed with saturated brine (10 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 7-[2-(5-methyl-2-(trans-1-

penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (0.39 g).

IR ν (neat) cm^{-1} ; 1743, 1505.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (3H, t, $J=7.0\text{Hz}$), 1.20-1.70 (2H, m), 2.00-2.40 (3H, m), 2.27 (3H, s), 2.50-3.20 (2H, m), 2.86 (2H, t, $J=6.7\text{Hz}$), 3.60-3.90 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.14 (2H, t, $J=6.7\text{Hz}$), 6.17 (1H, d, $J=16.0\text{Hz}$), 6.40-6.80 (1H, m), 6.54 (1H, d, $J=2.6\text{Hz}$), 6.69 (1H, dd, $J=8.3, 2.6\text{Hz}$), 6.99 (1H, d, $J=8.3\text{Hz}$).

(3) The compound (0.36 g) obtained in the above-mentioned (2) was dissolved in methylene chloride (5 ml), and sorbic chloride (0.13 g) and triethylamine (0.17 ml) were added. The mixture was stirred at room temperature for 30 min and ethyl acetate (30 ml) was added. The mixture was washed with 10% aqueous citric acid solution (15 ml) and saturated brine (15 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (0.4 g).

IR ν (neat) cm^{-1} ; 1740, 1655, 1628, 1605, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.95 (3H, t, $J=6.8\text{Hz}$), 1.20-1.70 (2H, m), 1.85 (3H, d, $J=5.0\text{Hz}$), 2.00-2.40 (2H, m), 2.04 (3H, s), 2.87 (2H, t, $J=6.7\text{Hz}$), 3.00-3.25 (2H, m), 3.59 (3H, s), 4.15 (2H, t, $J=6.7\text{Hz}$), 4.50-5.65 (3H, m), 6.00-6.90 (7H, m), 7.03 (1H, d, $J=8.2\text{Hz}$), 7.15-7.55 (1H, m).

(4) The compound (0.37 g) obtained in the above-mentioned (3) was dissolved in a mixture (9.4 ml) of tetrahydrofuran-methanol (3:1), and 1M aqueous lithium hydroxide solution (2.35 ml) was added and the mixture was stirred at 50°C for 30 min. The mixture was acidified with 10% aqueous citric acid solution, and the resulting mixture was concentrated under reduced pressure. The precipitated gummy material was extracted with

ethyl acetate, (50 ml), and the ethyl acetate layer was washed with saturated brine (30 ml), and dried (Na₂SO₄). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give the title compound (0.28 g).

IR ν (Nujol) cm⁻¹; 1728, 1651, 1616, 1531, 1504.

¹H-NMR (CDCl₃) δ (ppm); 0.92 (3H, t, J=6.8Hz), 1.20-1.75 (2H, m), 1.84 (3H, d, J=4.8Hz), 2.14 (2H, m), 2.22 (3H, s), 2.65 (2H, br-t), 2.80-3.50 (2H, m), 3.95 (2H, br-t), 4.60-5.10 (3H, m), 5.40-5.65 (1H, m), 6.00-6.80 (5H, m), 7.02 (1H, d, J=8.4Hz), 7.15-7.55 (1H, m), 9.80-10.50 (1H, br).

Example 3:
methyl 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

The compound (210 mg) obtained in Example 2(2) was dissolved in methylene chloride (2.1 ml), and 2-heptenoic acid (105 mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (160 mg) were added. The mixture was stirred at room temperature for 1 h. Ethyl acetate (30 ml) was added, and the mixture was washed with 10% aqueous citric acid solution (15 ml) and saturated brine (15 ml), and dried (Na₂SO₄). The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give methyl 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (200 mg).

The ¹H-NMR data were the same as those of the compound of Example 1(1).

The compounds of Examples 4-15 were synthesized in the same manner as in Examples 1-3.

Example 4:
2-(2-hexynoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-

yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 2237, 1717, 1684, 1616, 1576, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.85-1.20 (6H, m), 1.25-1.90 (4H, m),
2.00-2.50 (4H, m), 2.24 (3H, s), 2.60-3.50 (4H, m), 3.80-4.10
(2H, m), 4.35-5.20 (2H, m), 5.30-5.65 (1H, m), 6.18 (1H, d,
 $J=16.0\text{Hz}$) 6.45-6.85 (3H, m), 7.02 (1H, d, $J=7.9\text{Hz}$), 8.80-9.40
(1H, br).

Example 5

2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-

1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1729, 1652, 1615, 1575.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.83 (3H, br-d), 2.28 (3H, s), 2.82 (2H,
br-t), 2.90-3.50 (2H, m), 4.03 (2H, br-t), 4.60-5.10 (3H, m),
5.40-5.65 (1H, m), 6.00-6.80 (5H, m), 6.84 (1H, d, $J=16.5\text{Hz}$),
7.04 (1H, d, $J=8.4\text{Hz}$), 7.15-7.65 (7H, m), 9.40-10.20 (1H, br).

Example 6

2-(2-heptenoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-

1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1740, 1653, 1612, 1553, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.70-1.00 (3H, br); 1.10-1.75 (4H, m),
1.90-2.40 (2H, br), 2.29 (3H, s), 2.60-3.40 (4H, m), 3.75-4.20
(2H, m), 4.55-5.10 (2H, m), 5.40-5.70 (1H, m), 6.33 (1H, d,
 $J=15.7\text{Hz}$), 6.55-7.25 (5H, m), 7.30-7.70 (6H, m), 8.00-8.80 (1H,
br).

Example 7

2-(2-hexynoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-

1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 2235, 1734, 1630, 1580, 1528, 1504.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.96, 1.04 (3H, t, t, $J=6.7\text{Hz}$), 1.35-
1.80 (2H, m), 2.20-2.50 (2H, m), 2.29 (3H, s), 2.70-3.50 (4H,
m), 3.80-4.15 (2H, m), 4.55-5.20 (2H, m), 5.30-5.60 (2H, m),
6.45-6.70 (2H, m), 7.85 (1H, d, $J=16.5\text{Hz}$), 7.25-7.65 (6H, m),
7.90-8.60 (1H, br).

Example 8

7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-2-pentafluoropropionyl-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid.

IR ν (Nujol) cm^{-1} ; 1732, 1680, 1647, 1614, 1578, 1531, 1506.

$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{DMSO-d}_6$) δ (ppm); 2.34 (3H, s), 2.91 (2H, t,

$J=6.6\text{Hz}$), 3.10-3.30 (2H, m), 4.18 (2H, t, $J=6.6\text{Hz}$), 4.40-5.30

(3H, m), 6.50-6.90 (2H, m), 6.84 (1H, d, $J=16.5\text{Hz}$), 6.90-7.25

(2H, m), 7.30-7.60 (5H, m).

Example 9

2-(2-heptenoyl)-7-[2-(5-methyl-2-styrylthiazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1732, 1657, 1614, 1585, 1558, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.75-1.05 (3H, br), 1.10-1.75 (4H, br),

2.00-2.50 (4H, m), 2.38 (3H, s), 2.70-3.40 (4H, m), 3.90-4.30

(2H, m), 4.50-5.10 (2H, m), 5.35-5.70 (1H, m), 6.10-7.70 (13H, m).

Example 10

2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(1,3-pentadien-1-

yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid.

IR ν (Nujol) cm^{-1} ; 1730, 1648, 1616, 1456, 1377, 990.

$^1\text{H-NMR}$ (DMSO-d_6) δ (ppm); 1.83 (6H, br-s), 2.27 (3H, s), 2.6-3.4

(4H, m), 4.12 (2H, br-t), 4.2-5.0 (2H, m), 5.18 (1H, br-t),

5.9-7.4 (11H, m).

Example 11

2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-pentyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1728, 1653, 1616, 1574, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.87 (3H, t, $J=5.9\text{Hz}$), 1.10-1.40 (4H, m),

1.45-1.80 (2H, m), 1.84 (3H, d, $J=4.6\text{Hz}$), 2.20 (3H, s), 2.65

(2H, t, $J=8.1\text{Hz}$), 2.73 (2H, br-t), 3.93 (2H, br-t), 4.40-5.10

(3H, m), 5.45-5.70 (1H, m), 6.10-6.80 (5H, m), 7.03 (1H, d,

J=8.6Hz), 7.10-7.50 (1H, m), 9.10-10.00 (1H, br).

Example 12

7-[2-(2-cyclopentyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1733, 1652, 1615, 1568.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.0-2.0 (11H, m), 2.20 (3H, s), 2.77 (2H, t, J=6.0Hz), 2.8-3.4 (3H, m), 3.93 (2H, t, J=6.4Hz), 4.6-5.0 (2H, m), 5.54 (1H, br-t), 6.0-6.8 (5H, m), 7.02 (1H, d, J=8.4Hz), 7.1-7.6 (1H, m), 8.8-9.6 (1H, br).

Example 13

7-[2-(2-cyclohexyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1733, 1652, 1616, 1456, 1377, 1260, 999.

$^1\text{H-NMR}$ (DMSO-d_6) δ (ppm); 1.0-2.0 (13H, m), 2.20 (3H, s), 2.77 (2H, t, J=6.4Hz), 2.8-3.4 (3H, m), 4.09 (2H, t, J=6.4Hz), 4.2-5.0 (2H, m), 5.17 (1H, br-t), 5.9-7.3 (7H, m).

Example 14

2-(2-heptenoyl)-7-[2-(1-phenylethylideneaminoxy)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1732, 1716, 1651, 1574, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.75-1.05 (3H, m), 1.10-1.70 (4H, m), 2.00-2.40 (2H, m), 2.21 (3H, s), 2.80-3.30 (2H, m), 4.10-4.30 (2H, m), 4.40-5.10 (4H, m), 5.30-5.60 (1H, m), 6.15-7.15 (6H, m), 7.25-7.50 (3H, m), 7.60-7.80 (2H, m).

Example 15

2-(2-heptenoyl)-7-[2-(4-methyl-2-phenylsulfanyltiazol-5-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1726, 1612, 1582, 1502.

$^1\text{H-NMR}$ (DMSO-d_6) δ (ppm); 0.70-1.10 (3H, m), 1.20-1.70 (4H, m), 2.00-2.30 (2H, m), 2.29 (3H, s), 2.90-3.60 (5H, m), 4.04 (2H, t, J=5.9Hz), 4.35-4.95 (2H, m), 5.00-5.30 (1H, m), 6.35-6.90 (4H,

m), 7.09 (1H, d, J=7.9Hz), 7.35-7.70 (5H, m).

Example 16

7-[2-(2-benzoylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-
1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

5 (1) 2-(2-Aminothiazol-5-yl)ethyl methanesulfonate (2.43 g) and methyl 2-tert-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (2.17 g) were dissolved in N,N-dimethylformamide (50 ml), and cesium carbonate (5.20 g) was added. The mixture was stirred at 55°C for 15 h. To the
10 reaction mixture was added water (200 ml), and the mixture was extracted 3 times with ethyl acetate (100 ml). The ethyl acetate layer was washed twice with water (100 ml) and then with saturated brine (100 ml), and dried (Na₂SO₄). Ethyl acetate was evaporated under reduced pressure and the obtained
15 residue was purified by column chromatography to give methyl 7-(2-aminothiazol-5-yl)ethoxy-2-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (2.20 g).

¹H-NMR(CDCl₃) δ (ppm); 1.46, 1.51 (9H, s, s), 2.80-3.30 (4H, m), 3.61 (3H, s), 4.07 (2H, t, J=6.3Hz), 4.30-4.90 (4H, m), 4.95-
20 5.25 (1H, m), 6.55-6.90 (3H, m), 7.03 (1H, d, J=8.4Hz).

(2) The compound (500 mg) obtained in the above-mentioned (1) was dissolved in N,N-dimethylformamide (5.0 ml), and triethylamine (0.25 ml) and benzoyl chloride (0.16 ml) were added. The mixture was stirred at 55°C for 15 h. To the
25 reaction mixture was added water (20 ml), and the mixture was extracted 3 times with ethyl acetate (10 ml). The ethyl acetate layer was washed twice with water (20 ml) and then with saturated brine (20 ml), and dried (Na₂SO₄). Ethyl acetate was evaporated under reduced pressure and the obtained residue was
30 purified by column chromatography to give methyl 7-(2-benzoylaminothiazol-5-yl)ethoxy-2-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (535 mg).

IR ν (Nujol) cm⁻¹; 1746, 1684, 1605, 1582, 1555, 1535, 1506.

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20

¹H-NMR(CDCl₃) δ (ppm); 1.46, 1.51 (9H, s, s), 2.90-3.30 (5H, m), 3.61 (3H, s), 4.11 (2H, t, J=6.1Hz), 4.20-4.90 (2H, m), 4.95-5.25 (1H, m), 6.55-6.90 (3H, m), 7.04 (1H, d, J=7.9Hz), 7.30-7.70 (3H, m), 7.90-8.20 (2H, m).

5 (3) The compound (535 mg) obtained in the above-mentioned (2) was dissolved in formic acid (2.0 ml), and 8.78M hydrogen chloride - 2-propanol solution (0.30 ml) was added under ice-cooling. The mixture was stirred at the same temperature for 15 min. The reaction mixture neutralized with saturated
10 aqueous sodium hydrogen carbonate, extracted with chloroform (30 ml) and dried (Na₂SO₄). Chloroform was evaporated under reduced pressure to give methyl 7-(2-benzoylaminothiazol-5-yl)ethoxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (401 mg).

15 IR ν (Nujol) cm⁻¹; 3161, 1744, 1659, 1603, 1582, 1558, 1535, 1501.

¹H-NMR(CDCl₃) δ (ppm); 2.90-3.10 (2H, m), 3.19 (2H, t, J=6.1Hz), 3.60-3.80 (1H, m), 3.77 (3H, s), 4.00-4.30 (4H, m), 6.58 (1H, d, J=2.2Hz), 6.74 (1H, dd, J=2.2, 8.4Hz), 6.95-7.10 (2H, m), 7.30-
20 7.60 (3H, m), 7.85-8.10 (2H, m).

(4) The compound (400 mg) obtained in the above-mentioned (3) was dissolved in methylene chloride (5.0 ml), and 2-heptenoic acid (0.19 ml) and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (265 mg) were added under ice-cooling. The mixture was stirred at room temperature for 1 h, washed with 10% aqueous citric acid solution (10 ml) and then with saturated brine (30 ml), and dried (Na₂SO₄). Methylene
25 chloride was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give methyl 7-(2-benzoylaminothiazol-5-yl)ethoxy-2-(2-heptenoyl)-1,2,3,4-
30 tetrahydroisoquinoline-(3S)-carboxylate (495 mg).

IR ν (neat) cm⁻¹; 3165, 1740, 1661, 1616, 1558, 1533, 1506.

¹H-NMR(CDCl₃) δ (ppm); 0.80-1.10 (3H, m), 1.20-1.70 (4H, m),

2.00-2.50 (2H, m), 3.00-3.45, (4H, m), 3.60 (3H, s), 4.12 (2H, t, J=5.9Hz), 4.50-5.00 (2H, m), 5.40-5.60 (1H, m), 6.35 (1H, d, J=15.1Hz), 6.65-7.20 (4H, m), 7.35-7.70 (3H, m), 7.80-8.15 (2H, m).

(5). The compound (490 mg) obtained in the above-mentioned (4) was dissolved in a mixture (20 ml) of tetrahydrofuran-methanol (3:1), and 1M aqueous lithium hydroxide solution (3.0 ml) was added. The mixture was stirred at 50°C for 30 min and acidified with 10% aqueous citric acid solution. The solvent was evaporated under reduced pressure. The precipitated crystals were collected by filtration to give the title compound (342 mg).

IR ν (Nujol) cm^{-1} ; 1734, 1655, 1603, 1560, 1541, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.80-1.10 (3H, m), 1.20-1.70 (4H, m), 2.00-2.50 (2H, m), 2.80-3.40 (4H, m), 3.80-4.20 (2H, m), 4.50-5.05 (2H, m), 5.50-5.80 (1H, m), 6.05-7.20 (6H, m), 7.30-7.70 (3H, m), 7.80-8.15 (2H, m), 9.60-11.20 (1H, br).

The compound of Example 17 was synthesized in the same manner as in Example 16.

Example 17

7-[2-(2-butyrylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 3172, 1734, 1692, 1655, 1612, 1562, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, t, J=7.0Hz), 1.10-1.90 (6H, m), 2.10-2.60 (2H, m), 2.80-3.50 (4H, m), 3.80-4.30 (2H, m), 4.40-5.10 (2H, m), 5.55-5.80 (1H, m), 6.10-7.30 (6H, m), 9.60-11.20 (2H, br).

Example 18

methyl 7-[2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

(1) Methyl 2-tert-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (1.0 g) and 2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethyl

methanesulfonate (1.4 g) were dissolved in toluene (30 ml), and potassium carbonate (1.35 g) and tetraethylammonium fluoride hydrate (0.2 g) were added. The mixture was stirred at 80°C for 13 h. To the reaction mixture was added ethyl acetate (50 ml), and the mixture was washed successively with water (50 ml) and saturated brine (30 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 2-tert-butoxycarbonyl-7-[2-(5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-

(3S)-carboxylate (1.6 g).
 IR ν (neat) cm^{-1} ; 2957, 2928, 2872, 1746, 1701, 1614, 1533, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, d, $J=6.3\text{Hz}$), 1.46, 1.50 (9H, s, s), 1.50-2.00 (1H, m), 2.11 (2H, t, $J=6.8\text{Hz}$), 2.28 (3H, s), 2.87 (2H, t, $J=6.6\text{Hz}$), 3.00-3.25 (2H, m), 3.61 (3H, s), 4.15 (2H, t, $J=6.6\text{Hz}$), 4.45-5.25 (3H, m), 6.15 (1H, d, $J=15.8\text{Hz}$), 6.45-6.80 (3H, m), 7.01 (1H, d, $J=8.8\text{Hz}$).

(2) The compound (1.6 g) obtained in the above-mentioned (1) was dissolved in formic acid (8 ml), and 8.78M hydrogen chloride - 2-propanol solution (1.1 ml) was added under ice-cooling. The mixture was stirred at room temperature for 15 min. To the reaction mixture were added ethyl acetate and water (50 ml each). After neutralization with sodium bicarbonate, two layers were separated, and the obtained ethyl acetate layer was washed with saturated brine (30 ml) and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give the title compound (1.17 g).

IR ν (neat) cm^{-1} ; 3344, 2955, 2926, 2870, 1738, 1661, 1641, 1612, 1533, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, d, $J=6.3\text{Hz}$), 1.50-1.95 (1H, m), 2.11 (2H, t, $J=6.6\text{Hz}$), 2.12 (1H, br-s), 2.28 (3H, s), 2.87 (2H,

t, J=6.8Hz), 2.90-3.10 (2H, m), 3.55-3.90 (1H, m), 3.77 (3H, s), 4.06 (2H, s), 4.14 (2H, t, J=6.8Hz), 6.16 (1H, d, J=15.8Hz), 6.40-6.80 (3H, m), 7.00 (1H, d, J=8.4Hz).

Example 19

5 2-(2,4-hexadienoyl)-7-[2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

(1) The compound (1.15 g) obtained in Example 18 was dissolved in methylene chloride (20 ml), and sorbic acid chloride (0.45 g) and triethylamine (0.6 ml) were added. The mixture was stirred at room temperature for 15 min and methylene chloride (30 ml) was added. The mixture was washed with water and saturated brine (30 ml each), and dried (Na₂SO₄). Methylene chloride was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (1.36 g).

IR_v (neat) cm⁻¹: 1740, 1655, 1628, 1533, 1508.

20 ¹H-NMR(CDCl₃) δ (ppm): 0.94 (6H, d, J=6.4Hz), 1.50-1.95 (4H, m), 2.11 (2H, t, J=7.0Hz), 2.28 (3H, s), 2.87 (2H, t, J=6.6Hz), 3.00-3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J=6.6Hz), 4.50-5.15 (2H, m), 5.40-5.70 (1H, m), 6.00-6.90 (7H, m), 7.04 (1H, d, J=8.2Hz), 7.15-7.55 (1H, m).

25 (2) The compound (1.36 g) obtained in the above-mentioned (1) was dissolved in a mixture (16 ml) of tetrahydrofuran-methanol (3:1), and 1M aqueous lithium hydroxide solution (8.3 ml) was added. The mixture was stirred at room temperature for 30 min and acidified with 10% aqueous citric acid solution. The solution was concentrated under reduced pressure and the precipitated gummy material was extracted with ethyl acetate (50 ml). The ethyl acetate layer was washed with saturated brine (30 ml), and dried (Na₂SO₄). Ethyl acetate was evaporated

under reduced pressure to give the title compound (1.26 g).

IR ν (neat) cm^{-1} ; 2959, 2930, 2872, 1738, 1651, 1620, 1583, 1533, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.92 (6H, d, $J=6.4\text{Hz}$), 1.45-2.00 (1H, m),

1.84 (3H, d, $J=4.9\text{Hz}$), 2.09 (2H, t, $J=7.0\text{Hz}$), 2.23 (3H, s),

2.78 (2H, t, $J=6.4\text{Hz}$), 2.95-3.40 (2H, m), 4.00 (2H, t, $J=6.4\text{Hz}$),

4.30-5.65 (3H, m), 5.95-7.55 (9H, m)

Example 20

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(4-methyl-
trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylate

The compound (1.25 g) obtained in Example 19 was dissolved in methanol (7.0 ml), and tert-butylamine (0.55 ml) was added dropwise. Diisopropyl ether (70 ml) was added and the mixture was stirred at room temperature for 30 min. The precipitated crystals were collected by filtration to give the title compound (1.15 g).

IR ν (neat) cm^{-1} ; 2741, 2633, 2544, 1653, 1628, 1558, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.93 (6H, d, $J=6.6\text{Hz}$), 0.99 (9H, s),

1.60-2.00 (4H, m), 2.10 (2H, t, $J=6.8\text{Hz}$), 2.28 (3H, s), 2.86

(2H, t, $J=6.8\text{Hz}$), 2.90-3.40 (2H, m), 4.11 (2H, t, $J=6.8\text{Hz}$),

4.30-5.25 (3H, m), 6.00-7.50 (12H, m).

Example 21

methyl 7-(2-[2-(trans-2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

(1) Methyl 2-tert-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (2.93 g) and 2-[2-(trans-2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethyl methanesulfonate (4.29 g) were dissolved in toluene (90 ml), and potassium carbonate (3.95 g) and tetraethylammonium fluoride hydrate (0.75 g) were added. The mixture was stirred at 90°C for 16 h. To the reaction mixture was added ethyl acetate (30 ml), and the mixture was washed successively with

water (50 ml) and saturated brine (50 ml), and dried (Na_2SO_4).

The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column

chromatography to give methyl 2-tert-butoxycarbonyl-7-[2-

(trans-2-cyclopentylvinyl)-5-methyloxazol-4-yl]oxazol-4-

yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (3.9

g).

IR ν (neat) cm^{-1} ; 2955, 2970, 1742, 1699, 1614, 1533, 1506.

$^1\text{H-NMR}$ (CDCl_3), δ (ppm); 1.20-2.00 (17H, m), 2.27 (3H, s), 2.34-

2.74 (1H, m), 2.86 (2H, t, $J=6.6$ Hz), 2.99-3.20 (2H, m), 3.61

(3H, s), 4.12 (2H, t, $J=6.6$ Hz), 4.24-5.20 (3H, m), 6.15 (1H, d,

$J=16.1$ Hz), 6.61 (1H, dd, $J=16.1, 7.5$ Hz), 6.53-6.80 (2H, m),

7.01 (1H, d, $J=8.3$ Hz).

(2) The compound (3.89 g) obtained in the above-mentioned (1)

was dissolved in formic acid (9.7 ml), and 10M hydrogen

chloride - 2-propanol solution (2.28 ml) was added under ice-

cooling. The mixture was stirred at room temperature for 35

min and the reaction mixture was poured into a mixture (200 ml)

of diisopropyl ether - n-hexane (1:1) under ice-cooling. The

resulting oil was separated by decantation and dissolved in

ethyl acetate (100 ml). Water (100 ml) was added, and

neutralized with sodium bicarbonate. Two layers were separated,

and ethyl acetate layer was washed successively with water and

saturated brine (50 ml each), and dried (Na_2SO_4). Ethyl acetate

was evaporated under reduced pressure to give the title

compound (3.07 g).

IR ν (neat) cm^{-1} ; 3344, 2951, 2870, 2777, 2740, 1659, 1643,

1612, 1504.

$^1\text{H-NMR}$ (CDCl_3), δ (ppm); 1.20-1.97 (8H, m), 1.99 (1H, s), 2.27

(3H, s), 2.30-2.77 (1H, m), 2.86 (2H, t, $J=6.7$ Hz), 2.80-3.10

(2H, m), 3.60-3.83 (1H, m), 3.76 (3H, s), 3.95-4.34 (4H, m),

6.15 (1H, d, $J=16.0$ Hz), 6.41-6.80 (3H, m), 6.99 (1H, d, $J=8.4$

Hz).

Example 22

tert-butylamine 7-(2-[2-(trans-2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

(1) The compound (3.05 g) obtained in Example 21 was dissolved in methylene chloride (30 ml), and sorbic acid chloride (1.12 g) and triethylamine (1.35 ml) were added under ice-cooling.

The mixture was stirred at the same temperature for 20 min.

The reaction mixture was washed with 10% aqueous citric acid solution and saturated brine (each 20 ml), and dried (Na₂SO₄).

Methylene chloride was evaporated under reduced pressure, and

the obtained residue was purified by silica gel column

chromatography to give methyl 7-(2-[2-(trans-2-

cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-

hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

(2.49 g).

IR ν (neat) cm⁻¹: 3464, 2953, 2870, 1740, 1657, 1628, 1605, 1506.

¹H-NMR (CDCl₃) δ (ppm): 1.20-1.97 (8H, m), 1.85 (3H, d, J=4.8 Hz), 2.27 (3H, s), 2.40-2.75 (1H, m), 2.86 (2H, t, J=6.5 Hz), 3.00-3.22 (2H, m), 3.59 (3H, s), 4.14 (2H, t, J=6.5 Hz), 4.36-5.00 (2H, m), 5.40-5.60 (1H, m), 6.07-6.80 (5H, m), 6.15 (1H, d, J=16.1 Hz), 6.61 (1H, dd, J=16.1, 7.2 Hz), 7.03 (1H, d, J=8.4 Hz), 7.13-7.50 (1H, m).

(2) The compound (2.48 g) obtained in the above-mentioned (1) was dissolved in a mixture (60 ml) of tetrahydrofuran-methanol (3:1), and 1M aqueous lithium hydroxide solution (14.7 ml) was added. The mixture was stirred at room temperature for 50 min and acidified with 6M hydrochloric acid. The solution was concentrated under reduced pressure and the precipitated gummy material was extracted with ethyl acetate (30 ml). The ethyl acetate layer was washed with saturated brine (30 ml), and dried (Na₂SO₄). Ethyl acetate was evaporated under reduced

pressure and the obtained residue was dissolved in methanol (2.4 ml). After dropwise addition of tert-butylamine (1.0 ml), diisopropyl ether (30 ml) was added, and the mixture was stirred under ice-cooling for 1 h 20 min. The precipitated
 5 crystals were collected by filtration to give the title compound (2.41 g).

IR ν (Nujol) cm^{-1} ; 2731, 2631, 2544, 1653, 1626, 1553, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.99 (9H, s), 1.20-2.05 (11H, m), 2.27 (3H, s), 2.38-2.73 (1H, m), 2.85 (2H, t, $J=6.5$ Hz), 2.90-3.40
 10 (2H, m), 4.10 (2H, t, $J=6.5$ Hz), 4.26-5.20 (3H, m), 5.86-7.38 (12H, m).

Example 23

methyl 2-(2-heptenoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-
 15 (3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2955, 2928, 2872, 1740, 1661, 1622, 1533, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.75-2.15 (3H, m), 0.94 (6H, d, $J=6.4$ Hz), 1.20-2.00 (5H, m), 2.20-2.45 (2H, m), 2.11 (2H, t, $J=6.6$ Hz),
 20 2.28 (3H, s), 2.87 (2H, t, $J=6.8$ Hz), 3.00-3.325 (2H, m), 3.60 (3H, s), 4.15 (2H, t, $J=6.8$ Hz), 4.40-5.60 (3H, m), 6.16 (1H, d, $J=16.0$ Hz), 6.35-7.20 (6H, m).

Example 24

tert-butylamine 2-(2-heptenoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-
 25 tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 1661, 1616, 1558, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.75-2.20 (3H, m), 0.93 (6H, d, $J=6.4$ Hz), 1.02 (9H, s), 1.20-1.60 (4H, m), 1.60-1.95 (1H, m), 1.95-2.30
 30 (2H, m), 2.10 (2H, t, $J=6.6$ Hz), 2.28 (3H, s), 2.86 (2H, t, $J=6.8$ Hz), 3.00-3.40 (2H, m), 4.10 (2H, t, $J=6.8$ Hz), 4.40-5.20 (3H, m), 6.15 (1H, d, $J=16.1$ Hz), 6.10-7.20 (9H, m).

Example 25

methyl 7-{2-[2-(trans-1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 3346, 2955, 2928, 2872, 1742, 1661, 1612, 1504.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.72-1.06 (3H, m), 1.06-1.65 (4H, m), 1.96-2.40 (3H, m), 2.27 (3H, s), 2.80-3.02 (2H, m), 2.86 (2H, t, $J=6.7$ Hz), 3.57-3.74 (1H, m), 3.76 (3H, s), 3.91-4.10 (2H, m), 4.14 (2H, t, $J=6.7$ Hz), 6.16 (1H, d, $J=16.0\text{Hz}$), 6.39-6.79 (3H, m), 6.99 (1H, d, $J=7.5\text{Hz}$).

Example 26

methyl 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 3468, 3020, 2957, 2930, 2872, 1740, 1657, 1629, 1605, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.75-1.07 (3H, m), 1.20-1.60 (4H, m), 1.85 (3H, d, $J=5.0$ Hz), 2.08-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, $J=6.6$ Hz), 3.00-3.25 (2H, m), 3.60 (3H, s), 4.15 (2H, t, $J=6.6$ Hz), 4.35-5.10 (2H, m), 5.52 (1H, br-t), 5.96-6.84 (7H, m), 7.01 (1H, d, $J=8.4$ Hz), 7.15-7.50 (1H, m).

Example 27

tert-butylamine 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3400, 2745, 2637, 2548, 2220, 1651, 1626, 1556, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.75-1.16 (3H, m), 0.98 (9H, s), 1.20-1.60 (4H, m), 1.70-2.00 (3H, m), 2.07-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, $J=6.5\text{Hz}$), 2.88-3.30 (2H, m), 4.11 (2H, t, $J=6.5\text{Hz}$), 4.25-5.20 (3H, m), 5.90-7.40 (12H, m).

Example 28

methyl 7-{2-[5-methyl-2-(5-methyl-trans-1-hexen-1-yl)oxazol-4-

yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 3346, 2953, 2926, 2870, 2849, 1742, 1641, 1612, 1533, 1504.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.90 (6H, d, $J=6.1$ Hz), 1.15-1.73 (3H, m), 1.86 (1H, br-s), 2.04-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, $J=6.6$ Hz), 2.90-3.06 (2H, m), 3.55-3.75 (1H, m), 3.77 (3H, s), 3.90-4.10 (2H, m), 4.22 (2H, t, $J=6.6$ Hz), 6.17 (1H, d, $J=16.0$ Hz), 6.39-6.81 (3H, m), 6.99 (1H, d, $J=8.3$ Hz).

Example 29

methyl 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 3462, 2955, 2928, 2870, 1740, 1653, 1630, 1533, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.90 (6H, d, $J=6.2$ Hz), 1.14-1.72 (3H, m), 1.86 (3H, d, $J=5.0$ Hz), 2.05-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, $J=6.6$ Hz), 3.00-3.25 (2H, m), 3.60 (3H, s), 4.15 (2H, t, $J=6.6$ Hz), 4.39-5.20 (2H, m), 5.42-5.65 (1H, m), 6.00-6.87 (7H, m), 7.04 (1H, d, $J=8.1$ Hz), 7.18-7.51 (1H, m).

Example 30

tert-butylamine 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3400, 2735, 2635, 2550, 1657, 1634, 1558, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.90 (6H, d, $J=6.3$ Hz), 0.97 (9H, s), 1.20-1.70 (3H, m), 1.70-1.98 (3H, m), 2.06-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, $J=6.4$ Hz), 2.90-3.25 (2H, m), 4.10 (2H, t, $J=6.4$ Hz), 4.25-5.20 (3H, m), 5.72-7.38 (12H, m).

Example 31

methyl 7-{2-[5-methyl-2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 3344, 2957, 2930, 2872, 1742, 1647, 1612,

1504.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.95 (3H, t, $J=7.2\text{Hz}$), 1.20-1.72 (2H, m), 2.02 (3H, s), 2.03-2.30 (3H, m), 2.27 (3H, s), 2.88 (2H, t, $J=6.8\text{Hz}$), 2.90-3.10 (2H, m), 3.60-3.80 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.14 (2H, t, $J=6.8\text{Hz}$), 6.30-6.80 (3H, m), 6.99 (1H, d, $J=8.4\text{Hz}$).

Example 32

methyl 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-
 10 (3S)-carboxylate

IR ν (neat) cm^{-1} ; 3462, 2957, 2930, 2872, 1740, 1655, 1628, 1612, 1533, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.95 (3H, t, $J=7.0\text{Hz}$), 1.20-1.75 (2H, m), 1.86 (3H, d, $J=5.0\text{Hz}$), 2.00-2.30 (2H, m), 2.04 (3H, s), 2.28
 15 (3H, s), 2.89 (2H, t, $J=6.5\text{Hz}$), 3.02-3.25 (2H, m), 3.60 (3H, s), 4.15 (2H, t, $J=6.5\text{Hz}$), 4.36-5.00 (2H, m), 5.50 (1H, br-t), 5.92-6.85 (6H, m), 7.03 (1H, d, $J=8.1\text{Hz}$), 7.15-7.53 (1H, m).

Example 33

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-
 20 tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2748, 2637, 2544, 2220, 1651, 1624, 1600, 1553.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.80-1.08 (3H, m), 0.97 (9H, s), 1.11-
 25 1.70 (2H, m), 1.70-1.93 (3H, m), 1.93-2.35 (2H, m), 2.01 (3H, s), 2.27 (3H, s), 2.87 (2H, t, $J=6.7\text{Hz}$), 2.90-3.40 (2H, m), 4.10 (2H, t, $J=6.7\text{Hz}$), 4.24-5.20 (3H, m), 5.92-7.38 (11H, m).

Example 34

methyl 7-(2-[5-methyl-2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate
 30

IR ν (neat) cm^{-1} ; 2956, 2932, 2875, 1739, 1646, 1611, 1582, 1533, 1505.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.06 (3H, t, $J=7.5\text{Hz}$), 2.01 (3H, s),

2.10-2.45 (3H, m), 2.27 (3H, s), 2.70-3.20 (4H, m), 3.55-3.90 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.14 (2H, t, J=6.8Hz), 6.25-6.85 (3H, m), 6.99 (1H, d, J=8.6Hz).

Example 35

⁵ methyl 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 2961, 2933, 2875, 1739, 1652, 1627, 1606, 1534, 1506.

¹⁰ $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.06 (3H, t, J=7.5Hz), 1.85 (3H, d, J=5.0Hz), 2.01 (3H, s), 2.05-2.45 (2H, m), 2.28 (3H, s), 2.89 (2H, t, J=6.4 Hz), 3.00-3.40 (2H, m), 4.15 (2H, t, J=6.4 Hz), 4.30-5.65 (3H, m), 7.03 (1H, d, J=8.4Hz), 5.90-7.60 (7H, m).

Example 36

¹⁵ tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2733, 2635, 2550, 1657, 1634, 1611, 1558, 1506.

²⁰ $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.99 (9H, s), 1.05 (3H, t, J=7.5Hz), 1.65-1.95 (3H, m), 2.01 (3H, s), 2.05-2.45 (2H, m), 2.28 (3H, s), 2.87 (2H, t, J=6.7Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6.7Hz), 4.25-5.20 (3H, m), 5.90-8.30 (12H, m).

Example 37

²⁵ 7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-2-(2,2,3,3,3-pentafluoropropionyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 2725, 2509, 1917, 1732, 1682, 1614, 1589, 1531.

³⁰ $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.93 (3H, t, J=7.1Hz), 1.20-1.70 (2H, m), 2.00-2.38 (2H, m), 2.23 (3H, s), 2.59-2.87 (2H, m), 2.91-3.52 (2H, m), 3.64-4.00 (2H, m), 4.21-5.03 (2H, m), 5.03-5.47 (1H, m), 6.18 (1H, d, J=16.3Hz), 6.42-6.85 (3H, m), 7.05 (1H, d,

$J=8.4\text{Hz}$), 7.14-7.68 (1H, br).

Example 38

methyl 7-(2-[2-(trans-2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 2926, 2851, 1740, 1641, 1612, 1582, 1533, 1504.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.80-2.45 (11H, m), 2.27 (3H, s), 2.70-3.20 (2H, m), 2.86 (2H, t, $J=7.0\text{Hz}$), 3.55-3.85 (1H, m), 3.76 (3H, s), 4.04 (2H, s), 4.14 (2H, t, $J=6.8\text{Hz}$), 6.12 (1H, d, $J=16.0\text{Hz}$), 6.40-6.80 (3H, m), 6.99 (1H, d, $J=8.4\text{Hz}$).

Example 39

methyl 7-(2-[2-(trans-2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 1745, 1614, 1531, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.85-2.45 (14H, m), 2.27 (3H, s), 2.87 (2H, t, $J=6.8\text{Hz}$), 3.00-3.35 (2H, m), 3.59 (3H, s), 4.15 (2H, t, $J=6.8\text{Hz}$), 4.30-5.65 (3H, m), 6.00-7.55 (7H, m), 6.50 (1H, d, $J=6.4\text{Hz}$), 7.03 (1H, d, $J=8.4\text{Hz}$).

Example 40

tert-butylamine 7-(2-[2-(trans-2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2739, 2635, 2548, 1655, 1630, 1560, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.98 (9H, s), 1.00-2.40 (14H, m), 2.27 (3H, s), 2.85 (2H, t, $J=6.8\text{Hz}$), 2.90-3.30 (2H, m), 4.10 (2H, t, $J=6.8\text{Hz}$), 4.20-5.20 (3H, m), 5.80-7.45 (12H, m).

Example 41

2-cinnamoyl-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1728, 1647, 1612, 1578, 1533, 1506.

$^1\text{H-NMR}(\text{DMSO}-d_6)$ δ (ppm); 0.89 (3H, t, $J=7.3\text{Hz}$), 1.20-1.70 (2H, m), 1.95-2.25 (2H, m), 2.26 (3H, s), 2.65-2.95 (2H, m), 2.95-

91
3.15 (2H, m), 3.60-5.80 (1H, br), 3.95-4.35 (2H, m), 4.40-5.60 (3H, m), 6.19 (1H, d, J=16.5Hz), 6.33-6.90 (3H, m), 7.11 (1H, d, J=8.4Hz), 7.30-7.95 (7H, m).

Example 42

5 tert-butylamine 7-(2-[2-(3-ethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR, ν (Nujol) cm^{-1} ; 2735, 2633, 2544, 1653, 1624, 1599, 1551, 1506.

10 $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.87 (6H, t, J=7.2Hz), 0.96 (9H, s), 1.20-1.63 (4H, m), 1.63-2.10 (4H, m), 2.28 (3H, s), 2.86 (2H, t, J=6.8Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6.8Hz), 4.40-5.30 (3H, m), 5.80-7.60 (12H, m).

Example 43

15 tert-butylamine 7-(2-[2-(3,3-dimethyl-trans-1-buten-1-yl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3568, 2745, 2637, 2216, 1653, 1553.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.97 (18H, s), 1.60-2.00 (3H, m), 2.28 (3H, s), 2.86 (2H, t, J=6.5Hz), 2.90-3.35 (2H, m), 4.11 (2H, t, J=6.5 Hz), 4.28-5.20 (3H, m), 5.90-7.48 (12H, m).

Example 44

20 tert-butylamine 7-(2-[2-(3,3-dimethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3400, 2745, 2635, 2544, 2220, 1651, 1622, 1553.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.82 (3H, t, J=7.3Hz), 0.98 (9H, s), 1.05 (6H, s), 1.41 (2H, q, J=7.3Hz), 1.63-1.94 (3H, m), 2.28 (3H, s), 2.86 (2H, t, J=6.8Hz), 2.90-3.37 (2H, m), 4.11 (2H, t, J=6.8Hz), 4.23-5.20 (3H, m), 6.09 (1H, d, J=16.3Hz), 6.00-7.39 (11H, m).

Example 45

tert-butylamine 7-(2-[2-(4,4-dimethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

5 IR ν (Nujol) cm^{-1} ; 2733, 2635, 2550, 1657, 1634, 1611, 1558, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (9H, s), 1.01 (9H, s), 1.65-1.95 (3H, m), 2.09 (2H, d, $J=7.5\text{Hz}$), 2.28 (3H, s), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.90-3.30 (2H, m), 4.11 (2H, t, $J=6.6\text{Hz}$), 4.25-5.20 (3H, m), 5.90-7.35 (12H, m).

Example 46

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(3-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

15 IR ν (Nujol) cm^{-1} ; 2741, 2633, 2544, 1651, 1622, 1553, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.01 (9H, s), 1.08 (6H, d, $J=6.7\text{Hz}$), 1.65-1.95 (3H, m), 2.28 (3H, s), 2.35-2.70 (1H, m), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.85-3.30 (2H, m), 4.11 (2H, t, $J=6.6\text{Hz}$), 4.25-5.20 (3H, m), 5.85-8.00 (12H, m).

20 Example 47

tert-butylamine 2-(5-methyl-2-hexenoyl)-7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3398, 2741, 2635, 2548, 1661, 1614, 1553.

25 $^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.70-1.14 (18H, m), 1.14-2.20 (7H, m), 2.27 (3H, s), 2.85 (2H, br-t), 2.90-3.40 (2H, m), 4.10 (2H, br-t), 4.40-5.20 (3H, m), 5.80-7.10 (10H, m).

Example 48

tert-butylamine 2-(4,4-dimethyl-2-penthenoyl)-7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2741, 2633, 1622, 1556, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (3H, t, $J=7.5\text{Hz}$), 1.05 (9H, s),

1.10 (9H, s), 1.20-1.70 (2H, m), 2.05-2.45 (2H, m), 2.28 (3H, s), 2.86 (2H, t, J=6.3Hz), 2.95-3.30 (2H, m), 4.11 (2H, t, J=6.3Hz), 4.30-5.20 (3H, m), 5.00-6.00 (3H, br), 6.00-7.20 (7H, m).

5 **Example 49**

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(trans-2-thiophen-2-ylvinyl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3420, 2737, 2633, 2548, 1651, 1622, 1558, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.97 (9H, s), 1.83 (3H, br-d), 2.31 (3H, s), 2.89 (2H, t, J=6.3Hz), 2.90-3.23 (2H, m), 4.13 (2H, t, J=6.3Hz), 4.30-5.20 (3H, m), 6.00-6.78 (10H, m), 6.85-7.37 (2H, m), 7.49 (1H, d, J=16.4Hz).

15 **Example 50**

2-(2-heptenoyl)-7-(2-[5-methyl-2-phenylsulfanyloxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 2571, 1732, 1657, 1614, 1583, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.91 (3H, br-t), 1.10-1.70 (4H, m), 2.82 (2H, t, J=6.8Hz), 1.90-2.40 (2H, m), 2.22 (3H, s), 2.95-3.40 (2H, m), 4.07 (2H, t, J=6.8Hz), 4.20-5.65 (3H, m), 6.32 (1H, d, J=16.2Hz), 6.50-6.85 (4H, m), 7.04 (1H, d, J=7.7Hz), 7.20-7.65 (5H, m).

Example 51

25 tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[2-(trans-1-penten-1-yl)-5-propyloxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2731, 2633, 2546, 1630, 1553, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.91 (6H, t, J=7.0Hz), 0.96 (9H, s), 1.25-2.00 (7H, m), 2.20 (2H, q, J=7.0Hz), 2.60 (2H, t, J=7.0Hz), 2.87 (2H, t, J=6.6Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6.6Hz), 4.25-5.20 (3H, m), 5.80-7.40 (12H, m).

Example 52

tert-butylamine 2-(2,2-difluorobutyryl)-7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

⁵ IR ν (Nujol) cm^{-1} ; 2745, 2638, 2552, 1661, 1614, 1564, 1506.

¹H-NMR(CDCl₃) δ (ppm); 0.75-2.20 (6H, m), 1.25-1.70 (2H, m), 1.85-2.45 (4H, m), 0.93' (9H, s), 1.26-2.70 (11H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.6Hz), 2.95-3.25 (2H, m), 4.11 (2H, t, J=6.6Hz), 4.30-5.15 (3H, m), 6.17 (1H, d, J=16.3 Hz), 6.35-7.50
¹⁰ (7H, m).

Example 53

tert-butylamine 2-(4,4-difluoropentanoyl)-7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

¹⁵ IR ν (Nujol) cm^{-1} ; 3398, 2745, 2637, 2550, 1645, 1556.

¹H-NMR(CDCl₃) δ (ppm); 0.95 (3H, t, J=7.5 Hz), 0.99 (3H, s), 1.26-2.70 (11H, m), 2.28 (3H, s), 2.86 (2H, br-t), 3.00-3.41 (2H, m), 4.11 (2H, br-t), 4.36-4.70 (2H, m), 4.80-5.10 (1H, m), 5.57-6.14 (3H, br), 6.16 (1H, d, J=16.3 Hz), 6.41-6.80 (3H, m),
²⁰ 6.83-7.08 (1H, m).

Example 54

7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-2-(3,3,3-trifluoropropionyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

²⁵ IR ν (Nujol) cm^{-1} ; 2723, 2621, 1732, 1661, 1614, 1506.

¹H-NMR(CDCl₃) δ (ppm); 0.95 (3H, t, J=7.5Hz), 1.20-1.75 (2H, m), 2.23 (2H, t, J=6.8Hz), 2.34 (3H, s), 2.94 (2H, br-t), 3.00-3.60 (4H, m), 4.09 (2H, br-t), 4.30-5.50 (3H, m), 6.36 (1H, d, J=16.0Hz), 7.04 (1H, d, J=7.7Hz), 6.50-6.95 (3H, m), 8.93 (1H, br-s).
³⁰

Example 55

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[5-methyl-2-(2-methylsulfonyl)ethyl]oxazol-4-yl]ethoxy)-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2745, 2637, 2548, 1651, 1624, 1601, 1553, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.97 (9H, s), 1.65-2.00 (3H, m), 2.11 (3H, s), 2.25 (3H, s), 2.70-5.40 (6H, m), 2.85 (2H, t, $J=6.8\text{Hz}$), 4.10 (2H, t, $J=6.8\text{Hz}$), 4.25-5.20 (3H, m), 5.80-7.40 (12H, m).

Example 56

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-(5-methyl-2-[2-trans-(1-methylcyclohexen-1-yl)vinyl]oxazol-4-yl)ethoxy)-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2739, 2631, 2548, 1651, 1622, 1599, 1585, 1547, 1508.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.97 (9H, s), 1.05 (3H, s), 1.15-2.00 (13H, m), 2.28 (3H, s), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.90-3.40 (2H, m), 4.11 (2H, t, $J=6.6\text{Hz}$), 4.25-5.20 (3H, m), 5.85-7.50 (12H, m).

Example 57

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-(5-methyl-2-[2-trans-(1-methylcyclopentan-1-yl)vinyl]oxazol-4-yl)ethoxy)-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2739, 2633, 2544, 1634, 1549, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.99 (9H, s), 1.14 (3H, s), 1.30-2.05 (11H, m), 2.28 (3H, s), 2.86 (2H, t, $J=6.8\text{Hz}$), 2.90-3.40 (2H, m), 4.11 (2H, t, $J=6.8\text{Hz}$), 4.25-5.20 (3H, m), 5.80-7.45 (12H, m).

Example 58.

7-(2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

(1) Methyl 7-(2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (1.0 g) was dissolved in N,N-dimethylformamide (10 ml), and triethylamine (1.4 ml) and 5-bromo-1-pentene (1.2 ml)

were added. The mixture was stirred at room temperature for 40 h, and triethylamine (1.05 ml) and 5-bromo-1-pentene (0.89 ml) were added. The mixture was further stirred for 26 h. Ethyl acetate (20 ml) was added, and the mixture was washed twice
 5 with water (50 ml), 10% aqueous citric acid solution and saturated brine (10 ml each), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl
 10 7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate as an oil (0.89 g).

IR ν (neat) cm^{-1} , 3449, 2953, 2928, 2870, 1738, 1641, 1614, 1533, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, d, $J=6.3\text{Hz}$), 1.40-1.90 (3H, m),
 15 1.90-2.33 (4H, m), 2.27 (3H, s); 2.50-3.17 (6H, m), 3.65 (3H, s), 3.70-4.25 (5H, m), 4.80-5.13 (2H, m), 5.45-6.00 (1H, m), 6.16 (1H, d, $J=16.0\text{Hz}$), 6.36-6.79 (3H, m), 6.97 (1H, d, $J=8.4\text{Hz}$).

(2) The compound (0.8 g) obtained in the above-mentioned (1)
 20 was dissolved in a mixture (23 ml) of tetrahydrofuran-methanol (3:1), and 1M aqueous lithium hydroxide solution (5.66 ml) was added. The mixture was stirred for at room temperature 40 min and acidified with 10% aqueous citric acid solution. The solution was concentrated under reduced pressure and the
 25 precipitated gummy material was extracted with ethyl acetate (20 ml). The ethyl acetate layer was washed with saturated brine (20 ml) and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and n-hexane was added to the residue. The precipitated crystals were collected by filtration to give
 30 the title compound (0.74 g).

IR ν (Nujol) cm^{-1} ; 3400, 3057, 2725, 2664, 2565, 2494, 1626, 1551, 1508.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.93 (6H, d, $J=6.4\text{ Hz}$), 1.48-2.30 (7H,

(m), 2.28 (3H, s), 2.60-3.33 (6H, m), 3.72 (1H, br-t), 3.82-4.46 (4H, m), 4.80-5.20 (2H, m), 5.42-5.97 (1H, m), 6.15 (1H, d, J=16.1Hz), 6.40-6.90 (3H, m), 7.08 (1H, d, J=8.4Hz), 8.55-9.05 (1H, br)

5 **Example 59**

2-benzyl-7-(2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

(1) Methyl 2-benzyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylate (483 mg) and 2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethyl methanesulfonate (700 mg) were dissolved in toluene (15 ml), and potassium carbonate (674 mg) and tetraethylammonium fluoride hydrate (100 mg) were added.

The mixture was stirred at 90°C for 18 h. To the reaction mixture was added ethyl acetate (10 ml), and the mixture was washed successively with water (20 ml) and saturated brine (20 ml), and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to give methyl 2-benzyl-7-(2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (590 mg).

IR ν (neat) cm⁻¹; 3443, 3027, 2953, 2926, 2871, 2841, 1739, 1613, 1534, 1505.

¹H-NMR(CDCl₃) δ (ppm); 0.93 (6H, d, J=6.4 Hz), 1.48-2.00 (1H, m), 2.10 (2H, t, J=6.8 Hz), 2.26 (3H, s), 2.84 (2H, t, J=6.8 Hz), 3.08 (2H, d, J=4.6 Hz), 3.66 (3H, s), 3.70-4.30 (5H, m), 3.90 (2H, s), 6.15 (1H, d, J=16.1 Hz), 6.38-6.78 (3H, m), 6.98 (1H, d, J=8.2 Hz), 7.16-7.50 (5H, m).

(2) The compound of (1) (570 mg) obtained in the above-mentioned (1) was dissolved in a mixture (14 ml) of tetrahydrofuran-methanol (3:1), and 1M aqueous lithium hydroxide solution (3.5 ml) was added. The mixture was stirred at 40°C for 1.5 h and acidified with 6M hydrochloric acid. The

solution was concentrated under reduced pressure and the precipitated gummy material was extracted with ethyl acetate (15 ml). The ethyl acetate layer was washed with saturated brine (10 ml) and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and n-hexane was added to the obtained residue. The mixture was stirred under ice-cooling for 30 min, and the precipitated crystals were collected by filtration to give the title compound (445 mg).

IR ν (Nujol) cm^{-1} ; 3385, 3047, 1718, 1636, 1585, 1549, 1533, 1501.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.93 (6H, d, $J=6.4\text{Hz}$), 1.46-1.99 (1H, m), 2.10 (2H, t, $J=6.7\text{Hz}$), 2.27 (3H, s), 2.85 (2H, t, $J=6.8\text{Hz}$), 3.19 (2H, d, $J=6.1\text{Hz}$), 3.63-4.40 (5H, m), 4.03 (2H, s), 6.15 (1H, d, $J=15.8\text{Hz}$), 6.36-6.85 (3H, m), 7.06 (1H, d, $J=8.6\text{Hz}$), 7.20-7.60 (5H, m), 9.37 (1H, br-s).

Example 60

2-benzyl-7-{2-[2-(3,3-dimethyl-trans-1-buten-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 3420, 1680, 1614, 1506.

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ (ppm); 1.07 (9H, s), 2.23 (3H, s), 2.77 (2H, t, $J=6.3\text{Hz}$), 2.80-3.10 (2H, m), 3.20-4.60 (8H, m), 6.07 (1H, d, $J=16.5\text{Hz}$), 6.59 (1H, d, $J=16.5\text{Hz}$), 6.40-6.80 (2H, m), 7.01 (1H, $J=8.4\text{Hz}$), 7.32 (5H, br-s).

Example 61

tert-butylamine 2-(2,2-dimethylpropyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3398, 2746, 2637, 2554, 1641, 1612, 1543.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.87 (9H, s), 0.93 (6H, d, $J=6.6\text{Hz}$), 1.02 (9H, s), 1.48-2.00 (1H, m), 2.11 (2H, t, $J=6.8\text{Hz}$), 2.28 (3H, s), 2.48 (2H, d, $J=7.9\text{Hz}$), 2.60-3.20 (2H, m), 2.86 (2H, t, $J=6.8\text{Hz}$), 3.30-3.53 (1H, m), 4.00 (2H, dd, $J=16.6\text{Hz}$, 52.7Hz),

4.11 (2H, t, J=6.8Hz), 6.16 (1H, d, J=16.0Hz), 6.37-7.00 (4H, m), 6.90 (1H, d, J=8.1Hz).

Example 62

7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-2-(2,2,3,3,3-pentafluoropropyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1697, 1610, 1529, 1508.

$^1\text{H-NMR}$ (DMSO- d_6) δ (ppm); 0.89 (3H, t, J=7.3Hz), 1.20-1.70 (2H, m), 1.95-2.25 (2H, m), 2.25 (3H, s), 2.00-4.40 (1H, br), 2.79 (2H, m), 2.95-3.15 (2H, m), 3.30-4.40 (7H, m), 6.19 (1H, d, J=16.5Hz), 6.33-6.90 (3H, m), 7.02 (1H, d, J=8.1Hz).

Example 63

7-(2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-2-(3,3,3-trifluoropropyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 1616, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.93 (3H, t, J=6.8Hz), 1.30-1.75 (2H, m), 2.10-2.70 (4H, m), 2.27 (3H, s), 2.75-3.40 (6H, m), 3.60-4.20 (5H, m), 5.80-8.00 (1H, br), 6.10-6.80 (4H, m), 7.02 (1H, d, J=8.1Hz).

Example 64

2-(3-butenyl)-7-(2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid

IR ν (Nujol) cm^{-1} ; 3385, 3080, 2725, 2583, 1717, 1614, 1533, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.93 (6H, d, J=6.4Hz), 1.48-1.99 (1H, m), 2.11 (2H, t, J=6.7Hz), 2.28 (3H, s), 2.35-2.62 (2H, m), 2.70-3.35 (6H, m), 3.76 (1H, br-t), 3.85-4.46 (4H, m), 4.90-5.25 (2H, m), 5.45-5.98 (1H, m), 6.15 (1H, d, J=16.1Hz), 6.40-6.86 (3H, m), 7.08 (1H, d, J=8.2Hz), 8.60-9.00 (1H, br).

Example 65

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[2-(3-methoxy-trans-1-

propen-1-yl)-5-methyloxazol-4-yl]ethoxy)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2737, 1652, 1624, 1599, 1555, 1587, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.00 (9H, s), 1.85-2.00 (3H, m), 2.29
 5 (3H, s), 2.87 (2H, t, $J=6.8\text{Hz}$), 2.90-3.25 (2H, m), 3.38 (3H, s),
 3.95-4.20 (2H, m), 4.11 (2H, t, $J=6.8\text{Hz}$), 4.30-5.20 (3H, m),
 5.90-8.40 (12H, m).

Example 66

tert-butylamine 7-(2-[2-(5-fluoro-trans-1-penten-1-yl)-5-
 10 methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2735, 2631, 2544, 2432, 2365, 2212, 1651,
 1624, 1599, 1553, 1504.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.99 (9H, s), 1.50-2.10 (5H, m), 2.15-
 15 2.55 (2H, m), 2.28 (3H, s), 2.80-3.40 (2H, m), 2.86 (2H, t,
 $J=6.6\text{Hz}$), 4.11 (2H, t, $J=6.6\text{Hz}$), 4.47 (2H, dt, $J=47.0, 5.7\text{Hz}$),
 4.50-5.20 (3H, m), 5.80-6.80 (9H, m), 6.85-7.25 (2H, m).

Example 67

tert-butylamine 7-[2-(2-cyclopentylidenemethyl-5-methyloxazol-
 20 4-yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2737, 2631, 2544, 1653, 1624, 1587, 1553,
 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.96 (9H, s), 1.50-2.05 (7H, m), 2.28
 25 (3H, s), 2.25-2.55 (2H, m), 2.55-3.30 (4H, m), 2.87 (2H, t,
 $J=6.8\text{Hz}$), 4.12 (2H, t, $J=6.8\text{Hz}$), 4.25-5.20 (3H, m), 5.80-7.40
 (11H, m).

Example 68

tert-butylamine 7-[2-(2-cyclohexylidenemethyl-5-methyloxazol-4-
 30 yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2739, 2631, 2542, 1653, 1624, 1549, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.01 (9H, s), 1.40-2.00 (9H, m), 2.10-

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2.40 (2H, m), 2.27 (3H, s), 2.65-3.40 (6H, m), 2.86 (2H, t, J=6.6Hz), 4.12 (2H, t, J=6.6Hz), 4.25-5.20 (3H, m), 5.80-7.40 (11H, m), 5.93 (1H, s).

Example 69

5 tert-butylamine 2-cyclopentylideneacetyl-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2745, 2638, 2554, 1655, 1556, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, d, J=6.8Hz), 0.97 (9H, s), 1.43-2.00 (5H, m), 2.11 (2H, t, J=6.7Hz), 2.28 (3H, s), 2.30-2.8 (4H, m), 2.86 (2H, t, J=6.8Hz), 2.90-3.40 (2H, m), 4.11 (2H, t, J=6.8Hz), 4.20-5.20 (3H, m), 5.93-6.28 (1H, m), 6.40-6.80 (3H, m), 6.80-7.20 (4H, m).

Example 70 :

15 tert-butylamine 2-cyclohexylideneacetyl-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR- ν (Nujol) cm^{-1} , 2743, 2637, 2554, 2216, 1636, 1556, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.93 (6H, d, J=6.4Hz), 1.02 (9H, s), 1.33-1.80 (7H, m), 2.00-2.50 (6H, m), 2.28 (3H, s), 2.86 (2H, t, J=6.7Hz), 2.95-3.42 (2H, m), 4.11 (2H, t, J=6.7Hz), 4.27-5.20 (3H, m), 5.64 (1H, d, J=7.7Hz), 6.16 (1H, d, J=14.8Hz), 6.40-6.80 (3H, m), 6.80-7.30 (4H, m).

Example 71

25 methyl 7-{2-[2-(5-tert-butylsulfanyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 2928, 2864, 1740, 1638, 1612, 1578, 1533,

1504. $^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.32 (9H, s), 1.60-2.00 (2H, m), 1.98 (1H, br-s), 2.15-2.40 (2H, m), 2.27 (3H, s), 2.56 (2H, t, J=7.2Hz), 2.80-3.05 (2H, m), 2.86 (2H, t, J=6.7Hz), 3.55-3.80 (1H, m), 3.76 (3H, s), 4.04 (2H, br-s), 4.16 (2H, t, J=6.7Hz), 6.17 (1H, d,

J=16.0Hz); 6.40-6.80 (3H, m), 6.99 (1H, d, J=8.3Hz).

Example 72

methyl 7-(2-[2-(5-tert-butylsulfanyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-

5 tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 2957, 2926, 2862, 1740, 1655, 1612, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.32 (9H, s), 1.60-2.00 (5H, m), 2.15-2.40 (2H, m), 2.28 (3H, s), 2.57 (2H, t, J=7.5Hz), 2.87 (2H, t, J=6.6Hz), 3.00-3.25 (2H, m), 3.59 (3H, s), 4.15 (2H, t, J=6.6Hz),
 10 4.35-5.60 (3H, m), 5.90-6.85 (7H, m), 7.04 (1H, d, J=8.4Hz), 7.15-7.50 (1H, m).

Example 73

tert-butylamine 7-(2-[2-(5-tert-butylsulfanyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-

15 tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 2743, 2635, 2548, 1742, 1655, 1628, 1601, 1555, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.00 (9H, s), 1.32 (9H, s), 1.60-2.00 (5H, m), 2.15-2.40 (2H, m), 2.28 (3H, s), 2.56 (2H, t, J=7.2Hz), 2.86 (2H, t, J=6.3Hz), 2.90-3.35 (2H, m), 4.11 (2H, t, J=6.3Hz), 4.30-5.15 (3H, m), 5.90-7.35 (12H, m).

Example 74

methyl 7-(2-[2-(5-dimethylamino-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-

25 tetrahydroisoquinoline-(3S)-carboxylate

IR ν (neat) cm^{-1} ; 3404, 2949, 2860, 2818, 2770, 1743, 1655, 1626, 1603, 1533, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.40-1.95 (5H, m), 2.10-2.40 (4H, m), 2.23 (6H, s), 2.28 (3H, s), 2.87 (2H, t, J=6.6Hz), 3.05-3.25 (2H, m), 3.59 (3H, m), 4.14 (2H, t, J=6.6Hz), 4.60-5.00 (2H, m), 5.40-5.70 (1H, m), 6.00-6.80 (7H, m), 6.90-7.35 (2H, m).

Example 75

sodium 7-(2-[2-(5-dimethylamino-trans-1-penten-1-yl)-5-

methyloxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3381, 2766, 2725, 1651, 1595, 1535, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.40-1.95 (5H, m), 2.05-2.60 (4H, m),
 2.25 (9H, s), 2.65-3.10 (4H, m), 3.90-4.10 (2H, m), 4.40-4.80 (2H, m), 5.05-5.55 (1H, m), 5.80-6.75 (7H, m), 6.80-7.25 (2H, m).

Example 76

tert-butylamine 2-(2-hexenoyl)-7-(2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 1661, 1616, 1558, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.75-2.20 (3H, m), 0.93 (6H, d, $J=6.4\text{Hz}$),
 1.02 (9H, s), 1.20-1.60 (2H, m), 1.60-1.95 (1H, m), 1.95-2.30 (4H, m),
 2.10 (2H, t, $J=6.6\text{Hz}$), 2.27 (3H, s), 2.86 (2H, t, $J=6.8\text{Hz}$),
 3.00-3.40 (2H, m), 4.10 (2H, t, $J=6.8\text{Hz}$), 4.40-5.20 (3H, m),
 6.15 (1H, d, $J=16.1\text{Hz}$), 6.10-7.20 (9H, m).

Example 77

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3435, 2729, 2633, 2548, 2214, 1657, 1630, 1551, 1504.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, d, $J=6.6\text{Hz}$), 0.97 (9H, s), 1.60-1.90 (4H, m), 2.13 (2H, t, $J=6.8\text{Hz}$), 2.80-3.20 (2H, m), 3.03 (2H, t, $J=6.6\text{Hz}$),
 4.15 (2H, t, $J=6.6\text{Hz}$), 4.25-5.20 (3H, m), 6.00-7.30 (12H, m), 7.38 (1H, s).

Example 78

tert-butylamine 7-(2-[2-(trans-2-cyclopentylvinyl)oxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.99 (9H, s), 1.20-2.05 (11H, m), 2.38-2.73 (1H, m), 2.90-3.40 (2H, m), 2.94 (2H, t, $J=6.5\text{Hz}$), 4.14 (2H, t,

$J=6.5\text{Hz}$), 4.26-5.20 (3H, m), 5.86-7.38 (12H, m), 7.50 (1H, s).

Example 79

tert-butylamine 7-(2-[2-(trans-2-cyclohexylvinyl)oxazol-4-yl]ethoxy)-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.98 (9H, s), 1.00-2.40 (14H, m), 2.90-3.30 (2H, m), 2.94 (2H, t, $J=6.8\text{Hz}$), 4.14 (2H, t, $J=6.8\text{Hz}$), 4.20-5.20 (3H, m), 5.80-7.47 (12H, m), 7.49 (1H, s).

Example 80

tert-butylamine 2-(2-heptenoyl)-7-(2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.75-2.20 (3H, m), 0.93 (6H, d, $J=6.4\text{Hz}$), 1.02 (9H, s), 1.20-1.60 (4H, m), 1.60-1.95 (1H, m), 1.95-2.30 (2H, m), 2.10 (2H, t, $J=6.6\text{Hz}$), 2.95 (2H, t, $J=6.8\text{Hz}$), 3.00-3.40 (2H, m), 4.15 (2H, t, $J=6.8\text{Hz}$), 4.40-5.20 (3H, m), 6.15 (1H, d, $J=16.1\text{Hz}$), 6.10-7.20 (9H, m), 7.48 (1H, s).

Example 81

tert-butylamine 2-(2-hexenoyl)-7-(2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

IR ν (Nujol) cm^{-1} ; 3435, 2729, 2633, 2548, 2214, 1661, 1622, 1553, 1504.

$^1\text{H-NMR}(\text{DMSO}-d_6)$ δ (ppm); 0.80-1.00 (3H, m), 0.90 (6H, d, $J=6.2\text{Hz}$), 1.14 (9H, s), 1.20-1.90 (6H, m), 1.95-2.25 (2H, m), 2.70-3.40 (3H, m), 4.10-5.20 (8H, m), 6.10-6.85 (6H, m), 7.00 (1H, d, $J=8.4\text{Hz}$), 7.78 (1H, s).

Example 82

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[2-(trans-1-hexen-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.75-1.16 (3H, m), 0.98 (9H, s), 1.20-1.60 (4H, m), 1.70-2.00 (3H, m), 2.07-2.40 (2H, m), 2.88-3.30 (2H, m), 2.95 (2H, t, $J=6.5\text{Hz}$), 4.16 (2H, t, $J=6.5\text{Hz}$), 4.25-5.20 (3H, m), 5.90-7.40 (12H, m), 7.49 (1H, s).

5 **Example 83**

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.80-1.08 (3H, m), 0.97 (9H, s), 1.11-1.70 (2H, m), 1.70-1.93 (3H, m), 1.93-2.35 (2H, m), 2.01 (3H, s), 2.90-3.40 (2H, m), 2.96 (2H, t, $J=6.7\text{Hz}$), 4.14 (2H, t, $J=6.7\text{Hz}$), 4.24-5.20 (3H, m), 5.92-7.38 (11H, m), 7.50 (1H, s).

Example 84

15 tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.99 (9H, s), 1.05 (3H, t, $J=7.5\text{Hz}$), 1.65-1.95 (3H, m), 2.01 (3H, s), 2.05-2.45 (2H, m), 2.90-3.30 (2H, m), 2.96 (2H, t, $J=6.7\text{Hz}$), 4.15 (2H, t, $J=6.7\text{Hz}$), 4.25-5.20 (3H, m), 5.90-8.30 (13H, m).

Example 85

tert-butylamine 2-(2,4-hexadienoyl)-7-(2-[(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

25 $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.90 (6H, d, $J=6.3\text{Hz}$), 0.97 (9H, s), 1.20-1.70 (3H, m), 1.70-1.98 (3H, m), 2.06-2.40 (2H, m), 2.90-3.25 (2H, m), 2.95 (2H, t, $J=6.4\text{Hz}$), 4.15 (2H, t, $J=6.4\text{Hz}$), 4.25-5.20 (3H, m), 5.72-7.38 (12H, m), 7.50 (1H, s).

30 **Reference Example 1**

ethyl 2-tert-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

(1) 3,5-Diiodo-L-tyrosine dihydrate (25 g) was suspended in

conc. hydrochloric acid (250 ml), and 1,2-dimethoxyethane (18 ml) and 37% formalin (20 ml) were successively added. The mixture was heated to 75°C over 30 min. To the reaction mixture were added conc. hydrochloric acid (120 ml), 1,2-dimethoxyethane (9 ml) and 37% formalin (10 ml), and the mixture was stirred at 75°C for 18 h. The precipitated crystals were collected by filtration and washed with 1,2-dimethoxyethane (20 ml) to give 7-hydroxy-6,8-diiodo-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid hydrochloride (12.8 g).

IR ν (Nujol) cm^{-1} ; 1751, 1599, 1578.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 3.00-3.30 (2H, m), 4.05 (2H, s), 4.30 (1H, dd, $J=5.9, 9.5\text{Hz}$), 7.71 (1H, s).

(2) The compound (12.8 g) obtained in the above-mentioned (1) was suspended in ethanol (500 ml) and conc. hydrochloric acid (10 ml) was added. The mixture was refluxed for 15 h. Ethanol was evaporated under reduced pressure, and ethyl acetate (300 ml) was added. The mixture was washed with saturated aqueous sodium hydrogen carbonate (100 ml) and saturated brine (100 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure to give ethyl 7-hydroxy-6,8-diiodo-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (11.11 g).

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.29 (3H, t, $J=7.0\text{Hz}$), 2.80-3.00 (2H, m), 3.30-4.10 (5H, m), 4.23 (2H, q, $J=7.0\text{Hz}$), 7.46 (1H, s).

(3) 10% Pd-C (350 mg) was suspended in methanol (60 ml), and the compound (2.8 g) of (2) and triethylamine (2.0 ml) were added. The mixture was subjected to catalytic hydrogenation at room temperature and 3.0 kgf/cm^2 for 3 h. Pd-C was filtered off and methanol was evaporated under reduced pressure. Ethyl acetate (100 ml) was added to the obtained residue, and the mixture was washed with saturated brine (100 ml) and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure to give ethyl 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-

carboxylate (1.14 g).

IR ν (Nujol) cm^{-1} ; 1732, 1607, 1516.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.28 (3H, t, $J=7.0\text{Hz}$), 2.80-3.10 (3H, m), 3.60-3.80 (1H, m), 3.97 (2H, s), 4.05-4.20 (4H, m), 6.43 (1H, s), 6.50-6.80 (1H, m), 6.92 (1H, d, $J=8.4\text{Hz}$).

(4) The compound (1.13 g) obtained in the above-mentioned (3) was dissolved in tetrahydrofuran (20 ml) and di-tert-butyl dicarbonate (1.5 g) was added. The mixture was stirred at room temperature for 1 h and ethyl acetate (30 ml) was added. The mixture was washed with saturated brine (20 ml) and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (1.51 g).

IR ν (Nujol) cm^{-1} ; 3260, 1756, 1671, 1615, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.29 (3H, t, $J=7.0\text{Hz}$), 1.47 (9H, s), 3.08 (2H, d, $J=5.2\text{Hz}$), 4.21 (2H, q, $J=7.0\text{Hz}$), 4.41 (1H, d, $J=15.5\text{Hz}$), 4.60-5.25 (1H, m), 4.65 (1H, d, $J=15.5\text{Hz}$), 5.00-6.00 (1H, br), 6.50-6.80 (2H, m), 6.98 (1H, d, $J=8.1\text{Hz}$).

Reference Example 2

methyl 2-tert-butoxycarbonyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

The title compound was obtained in the same manner as in Reference Example 1.

IR ν (Nujol) cm^{-1} ; 3261, 1755, 1672, 1614, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.47 (9H, s), 3.08 (2H, d, $J=5.2\text{Hz}$), 3.63 (3H, s), 4.40 (1H, d, $J=16.5\text{Hz}$), 4.60-5.25 (1H, m), 4.66 (1H, d, $J=16.5\text{Hz}$), 5.60-6.60 (1H, br), 6.50-6.80 (2H, m), 6.99 (1H, d, $J=8.1\text{Hz}$).

Reference Example 3

methyl 2-(2,4-hexadienoyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

Methyl 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (1.24 g) was dissolved in methylene chloride (25

ml) and triethylamine (5.0 ml) was added, which was followed by dropwise addition of sorbic acid chloride (2.1 ml) under ice-cooling. This was stirred at the same temperature for 15 min, washed with 10% aqueous citric acid solution (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml) and saturated brine (20 ml), and dried (Na_2SO_4). Methylene chloride was evaporated under reduced pressure and the obtained residue was purified by column chromatography. The obtained oil (1.04 g) was dissolved in methanol (20 ml), and 1M aqueous lithium hydroxide solution (3.0 ml) was added by portions at room temperature. After acidification with 10% aqueous citric acid solution, the mixture was extracted with ethyl acetate (50 ml). The ethyl acetate layer was washed with saturated brine (20 ml) and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (0.65 g).

IR ν (neat) cm^{-1} ; 3184, 1734, 1576, 1506.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.84 (3H, d, $J=5.0\text{Hz}$), 2.80-3.40 (2H, m), 3.59 (3H, s), 4.30-5.10 (2H, m), 5.30-5.60 (1H, m), 5.70-6.50 (4H, m), 6.64 (1H, s), 6.68 (1H, d, $J=7.9\text{Hz}$), 6.99 (1H, d, $J=7.9\text{Hz}$), 7.15-7.50 (1H, m).

Reference Example 4

methyl 2-(2-heptenoyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate

Methyl 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylate (0.9 g) was dissolved in methylene chloride (10 ml), and 2-heptenoic acid (1.39 g) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (2.08 g) were added. The mixture was stirred at room temperature for 30 min. Methylene chloride (20 ml) was added, and the mixture was washed with 10% aqueous citric acid solution (20 ml) and saturated brine (20 ml), and dried (Na_2SO_4). Methylene chloride was evaporated under reduced pressure and the obtained residue

was purified by column chromatography to give the title compound (1.15 g).

IR ν (neat) cm^{-1} ; 3265, 1740, 1655, 1593, 1508.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.90 (3H, br-t), 1.10-1.70 (4H, m),
 1.90-2.40 (2H, m), 3.00-3.40 (2H, m), 3.59 (3H, s), 4.35-5.65
 (4H, m), 6.36 (1H, d, $J=15.2\text{Hz}$), 6.55-6.80 (1H, m), 6.64 (1H,
 s), 6.80-7.20 (1H, m), 6.99 (1H, d, $J=7.9\text{Hz}$).

Reference Example 5

2-(5-methyl-2-styryloxazol-4-yl)ethanol

(1) β -methyl L-aspartate (20 g) was suspended in methylene
 chloride (400 ml), and cinnamoyl chloride (18.14 g) was added.
 Triethylamine (53 ml) was added dropwise at -5°C and the
 mixture was stirred at the same temperature for 1.5 h. The
 reaction mixture was extracted 5 times with water (300 ml), and
 the aqueous layer was acidified with 6M hydrochloric acid and
 was extracted with ethyl acetate (500 ml). The ethyl acetate
 layer was washed with saturated brine (300 ml) and dried
 (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure
 and the obtained residue (13.3 g) was dissolved in toluene (100
 ml). Acetic anhydride (22.6 ml), N-methylmorpholine (21.1 ml)
 and 4-dimethylaminopyridine were added and the mixture was
 stirred at 65°C for 5 h. Saturated aqueous sodium hydrogen
 carbonate was added to the reaction mixture, neutralized and
 two layers were separated. The toluene layer was washed with
 saturated brine (100 ml) and dried (Na_2SO_4). Toluene was
 evaporated under reduced pressure, and the obtained residue
 (9.1 g) was dissolved in toluene (90 ml). Phosphorus
 oxychloride (9.2 ml) was added and the mixture was refluxed for
 6 h. The reaction mixture was poured into ice water,
 neutralized with potassium carbonate and two layers were
 separated. The toluene layer was washed with saturated brine
 (100 ml) and dried (Na_2SO_4). Toluene was evaporated under
 reduced pressure and the obtained residue was purified by

column chromatography to give methyl (5-methyl-2-styryloxazol-4-yl)acetate (1.31 g).

IR ν (neat) cm^{-1} ; 1742, 1641.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.33 (3H, s), 3.52 (2H, s), 3.73 (3H, s), 6.85 (1H, d, $J=16.2\text{Hz}$), 7.15-7.60 (6H, m).

(2) The compound (1.31 g) obtained in the above-mentioned (1) was dissolved in diethyl ether (25 ml), and lithium aluminum hydride (0.23 g) was added by portions at 0°C . The mixture was stirred at the same temperature for 20 min. Water (5 ml) was added, an insoluble material was filtered off and two layers were separated. The diethyl ether layer was washed with saturated brine (15 ml) and dried (Na_2SO_4). Diethyl ether was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (0.55 g).

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.31 (3H, s), 2.61 (2H, d, $J=6.0\text{Hz}$), 3.20-3.50 (1H, br), 3.84 (2H, d, $J=6.0\text{Hz}$), 6.84 (1H, d, $J=16.2\text{Hz}$), 7.20-7.60 (6H, m).

Reference Example 6

methyl (5-methyl-2-styryloxazol-4-yl)acetate

Cinnamamide (0.5 g) and methyl 4-bromo-3-oxopentanoate (0.71 g) were dissolved in N,N -dimethylformamide (2.5 ml) and the mixture was stirred 100°C for 15 h. Ethyl acetate (50 ml) was added, and the mixture was washed with water (100 ml) and then with saturated brine (100 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (0.1 g).

The IR and $^1\text{H-NMR}$ were the same as those in Reference Example 5(1).

The following compounds were synthesized in the same manner as in Reference Examples 5 and 6.

Reference Example 7

2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethanol

IR ν (neat) cm^{-1} ; 3350, 1664, 1654, 1641, 1534.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.95 (3H, t, $J=7.0\text{Hz}$), 1.20-1.80 (2H, m), 2.00-2.40 (2H, m), 2.25 (3H, s), 2.64 (2H, t, $J=5.7\text{Hz}$), 2.70-3.20 (1H, br), 3.86 (2H, t, $J=5.7\text{Hz}$), 6.17 (1H, d, $J=8.0\text{Hz}$), 6.64 (1H, dt, $J=6.6, 8.0\text{Hz}$).

Reference Example 8.

2-(5-methyl-2-pentyloxazol-4-yl)ethanol

IR ν (neat) cm^{-1} ; 3341, 1576.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 0.90 (3H, br-t), 1.20-1.50 (4H, m), 1.50-1.95 (2H, m), 2.21 (3H, s), 2.45-2.80 (4H, m), 3.09 (1H, br-s), 3.85 (2H, t, $J=5.7\text{Hz}$).

Reference Example 9.

2-(2-cyclopentyl-5-methyloxazol-4-yl)ethanol

IR ν (neat) cm^{-1} ; 3341, 1572.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.40-2.30 (8H, m), 2.21 (3H, s), 2.61 (2H, t, $J=6.0\text{Hz}$), 2.95-3.30 (1H, m), 3.36 (1H, br-s), 3.84 (2H, t, $J=6.0\text{Hz}$).

Reference Example 10

2-(2-cyclohexyl-5-methyloxazol-4-yl)ethanol

IR ν (neat) cm^{-1} ; 3360, 1742, 1570, 1450.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 1.10-2.40 (11H, m), 2.21 (3H, s), 2.60-3.00 (1H, m), 2.61 (2H, t, $J=5.8\text{Hz}$), 3.09 (1H, br-s), 3.84 (2H, t, $J=5.8\text{Hz}$).

Reference Example 11

2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethyl

methanesulfonate

2-[5-Methyl-2-(1-penten-1-yl)oxazol-4-yl]ethanol (1.03 g) was dissolved in methylene chloride (10 ml), and triethylamine (1.03 ml) was added. Methanesulfonyl chloride (0.41 ml) was added dropwise at 0°C , and the mixture was stirred at room temperature for 30 min. Ethyl acetate (100 ml) was added, and the mixture was washed with 10% aqueous citric acid solution

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(100 ml) and then with saturated brine (100 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the title compound (1.1 g).

IR (neat) cm^{-1} ; 1654, 1643, 1551, 1534.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.90 (3H, t, $J=7.2\text{Hz}$), 1.20-1.80 (2H, m), 2.00-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, $J=6.7\text{Hz}$), 2.94 (3H, s), 4.45 (2H, t, $J=6.7\text{Hz}$), 6.16 (1H, d, $J=16.0\text{Hz}$), 6.69 (1H, dt, $J=16.0, 6.6\text{Hz}$).

Reference Example 12

10 2-(5-methyl-2-styrylthiazol-4-yl)ethyl methanesulfonate

(1) Cinnamamide (3.27 g) was dissolved in tetrahydrofuran (33 ml), and Lawesson's reagent (4.94 g) was added. The mixture was refluxed for 3 h and methyl 4-bromo-3-oxopentanoate (6.97 g) was added. The mixture was further refluxed for 11 h.

15 Tetrahydrofuran was evaporated under reduced pressure and ethyl acetate (300 ml) was added to the obtained residue. The mixture was washed with water (200 ml) and then with saturated brine (200 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was
20 purified by column chromatography to give methyl (5-methyl-2-styrylthiazole-4-yl)acetate (2.9 g).

IR (Nujol) cm^{-1} ; 1732, 1595, 1573, 1537.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.41 (3H, s), 3.72 (3H, s), 3.75 (2H, s), 7.15-7.60 (7H, m).

25 (2) The compound (2.85 g) obtained in the above-mentioned (1) was dissolved in toluene (16.7 ml), and 1.5M diisobutyl aluminum hydrate toluene solution (16.7 ml) was added dropwise at -10°C . The mixture was stirred at the same temperature for 1 h and water (5 ml) was added. An insoluble material was
30 filtered off and two layers were separated. The toluene layer was washed with saturated brine (10 ml) and dried (Na_2SO_4). Toluene was evaporated under reduced pressure and the obtained crude 2-(5-methyl-2-styrylthiazol-4-yl)ethanol (2.8 g) was

dissolved in methylene chloride (30 ml). Triethylamine (1.89 ml) was added, and methanesulfonyl chloride (0.97 ml) was added dropwise at 0°C. The mixture was stirred at room temperature for 20 min. Ethyl acetate (200 ml) was added, and the mixture was washed with 10% aqueous citric acid solution (200 ml) and then with saturated brine (100 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (1.1 g).

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm); 2.42 (3H, s), 2.91 (3H, s), 3.11 (2H, t, $J=6.6\text{Hz}$), 4.57 (2H, t, $J=6.6\text{Hz}$), 7.00–7.65 (7H, m).

Reference Example 13

2-[(1-phenylethylidene)aminoxy]ethanol

Acetophenone oxime (1.00 g) and 2-(2-bromoethoxy)-tetrahydropyran (3.09 g) were dissolved in N,N -dimethylacetamide (30 ml), and potassium carbonate (7.16 g) was added. The mixture was stirred at 80°C for 19 h. After allowing to cool, water (100 ml) was added to the reaction mixture. The mixture was extracted twice with ethyl acetate (50 ml). The ethyl acetate layers were combined, washed with water (50 ml) and then with saturated brine (50 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give a colorless oil (2.01 g). The obtained oil (1.99 g) was dissolved in methanol (30 ml), and p -toluenesulfonic acid monohydrate (1.73 g) was added. The mixture was stirred at room temperature for 1 h. Methanol was evaporated under reduced pressure and saturated aqueous sodium hydrogen carbonate solution (30 ml) was added. The mixture was extracted twice with ethyl acetate (30 ml). The ethyl acetate layers were combined and washed with saturated aqueous sodium hydrogen carbonate solution (50 ml) and then with saturated brine (50 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated

under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (1.09 g).

IR ν (neat) cm^{-1} ; 3700-3100, 1445, 1369, 1315, 1043, 762, 694, 559.

¹H-NMR(CDCl_3) δ (ppm); 2.27 (3H, s), 3.8-4.1 (2H, m), 4.2-4.5 (2H, m), 7.2-7.5 (3H, m), 7.5-7.8 (2H, m).

The following compounds were synthesized in the same manner as in Reference Example 11.

Reference Example 14

2-[(1-phenylethylidene)aminoxy]ethyl methanesulfonate

IR ν (Nujol) cm^{-1} ; 1354, 1177, 1069, 1018, 924, 804, 764, 696, 529.

¹H-NMR(CDCl_3) δ (ppm); 2.26 (3H, s), 3.02 (3H, s), 4.3-4.7 (4H, m), 7.2-7.5 (3H, m), 7.5-7.8 (2H, m).

Reference Example 15

2-(4-methyl-2-phenylsulfanyltiazol-5-yl)ethyl methanesulfonate

(1) Thiophenol (1.90 ml) was dissolved in N,N-dimethylformamide (10 ml). Sodium hydride (60% oil suspension, 740 mg) was added by portions under ice-cooling, and the mixture was stirred at room temperature for 15 min. Thereafter, a solution of ethyl 2-chloro-4-methylthiazole-5-carboxylate (3.05 g) in N,N-dimethylformamide (10 ml) was added dropwise, and the mixture was stirred at the same temperature for 20 min. Water (50 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (50 ml). The ethyl acetate layer was washed twice with water (50 ml) and then with saturated brine (30 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give ethyl 4-methyl-2-phenylsulfanyltiazole-5-carboxylate (3.85 g).

IR ν (neat) cm^{-1} ; 1713, 1531.

¹H-NMR(CDCl_3) δ (ppm); 1.28 (3H, t, $J=7.2\text{Hz}$), 2.67 (3H, s), 4.24 (2H, t, $J=7.2\text{Hz}$), 7.40-7.80 (5H, m).

(2) The compound (3.85 g) obtained in the above-mentioned (1) was dissolved in tetrahydrofuran (80 ml), and lithium aluminum hydride (630 mg) was added under ice-cooling by portions. The mixture was stirred at the same temperature for 15 min. Water (20 ml) and ethyl acetate (50 ml) were added, and an insoluble material was filtered off. Two layers were separated, and the ethyl acetate layer was washed with saturated brine (20 ml) and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure, and the obtained residue purified by column chromatography to give 4-methyl-2-phenylsulfanyltiazole-5-methanol (3.25 g).

IR ν (neat) cm^{-1} ; 3265, 1582, 1555.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.31 (3H, s), 2.50 (1H, s), 4.65 (2H, s), 7.30-7.70 (5H, m).

(3) The compound (7.30 g) obtained in the above-mentioned (2) was dissolved in methylene chloride (100 ml). Triethylamine (6.40 ml) was added and methanesulfonyl chloride (2.90 ml) was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 30 min. The reaction mixture was washed with cold water (20 ml) and dried (Na_2SO_4). Methylene chloride was evaporated under reduced pressure, and the obtained residue was dissolved in acetonitrile (100 ml). Sodium cyanide (2.26 g) and 18-crown-6 (1.50 g) were added, and the mixture was stirred at 60°C for 2 h. Acetonitrile was evaporated under reduced pressure and ethyl acetate (100 ml) was added to the obtained residue. The mixture was washed twice with water (50 ml) and then with saturated brine (30 ml), and dried (Na_2SO_4). Ethyl acetate was evaporated under reduced pressure, and the obtained residue was purified by column chromatography to give (4-methyl-2-phenylsulfanyltiazol-5-yl)acetonitrile (2.80 g).

IR ν (neat) cm^{-1} ; 2254, 1582, 1555.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.36 (3H, s), 3.68 (2H, s), 7.40-7.70 (5H,

m).

(4) The compound (2.80 g) obtained in the above-mentioned (3) was dissolved in conc. hydrochloric acid (5.6 ml) and the mixture was stirred at 100°C for 20 min. Methanol (120 ml) was added to the reaction mixture and the mixture was refluxed for 1 h. Methanol was evaporated under reduced pressure and ethyl acetate (50 ml) was added to the obtained residue. The mixture was washed with water (50 ml), saturated aqueous sodium hydrogen carbonate (30 ml) and then with saturated brine (30 ml), and dried (Na₂SO₄). Ethyl acetate was evaporated under reduced pressure to give methyl (4-methyl-2-phenylsulfanyltiazol-5-yl)acetate (2.77 g).

IR ν (neat) cm^{-1} ; 1740.

¹H-NMR(CDCl₃) δ (ppm); 2.33 (3H, s), 3.64 (2H, s), 3.69 (3H, s), 6.30-6.70 (5H, m).

(5) The compound (2.77 g) obtained in the above-mentioned (4) was dissolved in tetrahydrofuran (55 ml), and lithium aluminum hydride (376 mg) was added by portions under ice-cooling. The mixture was stirred at the same temperature for 15 min. Water (20 ml) and ethyl acetate (50 ml) were added, and an insoluble material was filtered off. Two layers were separated and the ethyl acetate layer was washed with saturated brine (20 ml) and dried (Na₂SO₄). Ethyl acetate was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give 2-(4-methyl-2-phenylsulfanyltiazol-5-yl)ethanol (2.49 g).

IR ν (neat) cm^{-1} ; 3302.

¹H-NMR(CDCl₃) δ (ppm); 1.60-2.00 (1H, br), 2.33 (3H, s), 2.89 (2H, t, J=6.1Hz), 3.75 (2H, t, J=6.1Hz), 7.30-7.70 (5H, m).

(6) The compound (2.49 g) obtained in the above-mentioned (5) was dissolved in methylene chloride (25 ml), and triethylamine (2.0 ml) was added. Methanesulfonyl chloride (0.93 ml) was added dropwise, and after under ice-cooling, the mixture was stirred

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at the same temperature for 30 min. The mixture was washed with 10% aqueous citric acid solution (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml) and then with saturated brine (20 ml), and dried (Na_2SO_4). Methylene chloride was evaporated under reduced pressure, and the obtained residue was purified by column chromatography to give the title compound (1.82 g).

IR ν (neat) cm^{-1} ; 1582, 1551.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.34 (3H, s), 2.92 (3H, s), 3.09 (2H, t, $J=6.6\text{Hz}$), 4.26 (2H, t, $J=6.6\text{Hz}$), 7.30-7.80 (5H, m).

Reference Example 16

methyl 2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]acetate

5-Methyl-trans-2-hexanamide (5.7 g) was suspended in toluene (35 ml) and 4-bromopropionylmethyl acetate (14.0 g) was added. The mixture was refluxed for 14 h. Ethyl acetate (50 ml) was added, and the mixture was washed successively with water (50 ml) and saturated brine (50 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (3.36 g).

IR ν (neat) cm^{-1} ; 2957, 2928, 2870, 1746, 1643, 1551.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, d, $J=6.3\text{Hz}$), 1.50-2.10 (1H, m), 2.11 (2H, t, $J=6.9\text{Hz}$), 2.27 (3H, s), 3.48 (2H, s), 3.71 (3H, s), 6.17 (1H, d, $J=16.0\text{Hz}$), 6.61 (1H, dt, $J=6.9\text{Hz}$, 16.0Hz).

Reference Example 17

methyl 2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]acetate

(1) β -Methyl L-aspartate (44.68 g) was dissolved in water (220 ml), and sodium carbonate (42.54 g) was added. Tetrahydrofuran (110 ml) was added and 5-methyl-trans-2-hexenoyl chloride (42.8 g) was added dropwise. The mixture was stirred at room temperature for 15 h and water (220 ml) was added. The mixture

1 was washed with ethyl acetate (110 ml), and the aqueous layer
 was adjusted to pH 2 with conc. hydrochloric acid and extracted
 with ethyl acetate (400 ml). The ethyl acetate layer was
 washed successively with water and saturated brine (150 ml
 5 each), and dried (Na_2SO_4). Ethyl acetate was evaporated under
 reduced pressure to give an oil (59.7 g). The obtained oil was
 dissolved in toluene (220 ml), and acetic anhydride (60 ml),
 pyridine (52 ml) and 4-dimethylaminopyridine (5.2 g) were added.
 The mixture was stirred at 65°C for 5 h. The reaction mixture
 10 was washed with water (300 ml) and 1M hydrochloric acid (500
 ml). Water (300 ml) was added to the toluene layer and the
 mixture was neutralized with sodium bicarbonate. Two layers
 were separated, and the toluene layer was washed with saturated
 brine (200 ml) and dried (Na_2SO_4). Toluene was evaporated under
 15 reduced pressure and n-hexane was added to the obtained residue.
 The precipitated crystals were collected by filtration to give
 methyl 3-(5-methyl-trans-2-hexenoylamino)-4-oxo-pentanoate
 (27.42 g).

IR ν (neat) cm^{-1} ; 3329, 1747, 1720, 1666, 1626, 1531.

20 $^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.93 (6H, d, $J=6.4\text{Hz}$), 1.50-2.00 (1H, m),
 2.09 (2H, t, $J=7.0\text{Hz}$), 2.25 (3H, s); 2.78, 3.06 (2H, ABq, $J=4.4$,
 17.2Hz); 3.69 (3H, s), 4.70-4.95 (1H, m), 5.83 (1H, d,
 $J=15.1\text{Hz}$), 6.45-7.00 (1H, br), 6.88 (1H, dt, $J=7.2\text{Hz}$, 15.1Hz).

(2) The compound (0.8 g) obtained in the above-mentioned (1)
 25 was the above-mentioned (1) was dissolved in toluene (5.6 ml),
 and phosphorus oxychloride (0.58 ml) was added. The mixture
 was refluxed for 1 h. The reaction mixture was poured into ice
 water (10 ml), and after neutralization with sodium bicarbonate,
 two layers were separated. The toluene layer was washed with
 30 saturated brine (10 ml) and dried (Na_2SO_4). Toluene was
 evaporated under reduced pressure and the obtained residue was
 purified by column chromatography to give the title compound
 (0.9 g).

The IR and ^1H -NMR were the same as those in Reference Example 16.

Reference Example 18

2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethanol

5 The compound (3.34 g) of Reference Example 16 was dissolved in toluene (30 ml) and 1.5M diisobutylaluminum hydride toluene solution (37.5 ml) was added dropwise at -70°C . The mixture was stirred at -70°C to -40°C for 1 h. The reaction mixture was poured into water (100 ml) and an insoluble
10 material was filtered off, after which two layers were separated. The toluene layer was washed with saturated brine (50 ml) and dried (Na_2SO_4). Toluene was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (1.75 g).
15 IR ν (neat) cm^{-1} ; 3346, 2957, 2926, 2870, 1661, 1641, 1533.
 ^1H -NMR (CDCl_3) δ (ppm); 0.94 (6H, d, $J=6.4\text{Hz}$), 1.50-2.10 (1H, m), 2.11 (2H, t, $J=7.0\text{Hz}$), 2.25 (3H, s), 2.71 (2H, t, $J=5.9\text{Hz}$), 2.81 (1H, br-s), 3.86 (2H, t, $J=5.9\text{Hz}$), 6.16 (1H, d, $J=16.0\text{Hz}$),
.. 6.62 (1H, dt, $J=7.0, 16.0\text{Hz}$).

20 **Reference Example 19**

2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethyl methanesulfonate

The compound (1.73 g) of Reference Example 18 was dissolved in methylene chloride (20 ml) and triethylamine (2.3
25 ml) was added. Methanesulfonyl chloride (0.77 ml) was added dropwise at 0°C and the mixture was stirred at room temperature for 20 min. Methylene chloride (30 ml) was added, washed with 10% aqueous citric acid solution (30 ml) and then with saturated brine (30 ml), and dried (Na_2SO_4). Methylene chloride
30 was evaporated under reduced pressure and the obtained residue was purified by column chromatography to give the title compound (2.21 g).
IR ν (neat) cm^{-1} ; 2959, 2928, 2870, 1643, 1535.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.94 (6H, d, $J=6.4\text{Hz}$), 1.50-2.10 (1H, m), 2.12 (2H, t, $J=7.0\text{Hz}$), 2.27 (3H, s), 2.87 (2H, t, $J=6.7\text{Hz}$), 2.94 (3H, s), 4.45 (2H, t, $J=6.6\text{Hz}$), 6.15 (1H, d, $J=15.8\text{Hz}$), 6.62 (1H, dt, $J=7.0, 15.8\text{Hz}$).

5 The following compounds were synthesized in the same manner as in Reference Example 19.

Reference Example 20

2-[2-(trans-2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethyl methanesulfonate

10 IR ν (neat) cm^{-1} ; 2926, 2853, 1736, 1643, 1533.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.85-2.50 (11H, m), 2.26 (3H, s), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.94 (3H, s), 4.44 (2H, t, $J=6.6\text{Hz}$), 6.11 (1H, d, $J=16.1\text{Hz}$), 6.46 (1H, dd, $J=6.6, 16.1\text{Hz}$).

Reference Example 21

15 2-[2-(trans-1-hepten-1-yl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 3628, 3420, 2959, 2930, 2860, 1738, 1643, 1576, 1533.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.75-1.10 (3H, m), 1.10-1.67 (4H, m),
20 2.04-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, $J=6.7\text{Hz}$), 2.94 (1H, s), 4.45 (2H, t, $J=6.7\text{Hz}$), 6.16 (1H, d, $J=16.0\text{Hz}$), 6.64 (1H, dt, $J=16.0\text{Hz}, 6.8\text{Hz}$).

Reference Example 22

2-[2-(5-methyl-trans-2-hexen-1-yl)5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 3632, 3410, 2957, 2928, 2870, 1661, 1643, 1535.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.91 (6H, d, $J=6.2\text{Hz}$), 1.13-1.90 (3H, m), 2.00-2.22 (2H, m), 2.26 (3H, s), 2.86 (2H, t, $J=6.7\text{Hz}$),
30 2.94 (3H, s), 4.45 (2H, t, $J=6.7\text{Hz}$), 6.20 (1H, d, $J=15.7\text{Hz}$), 6.62 (1H, dt, $J=15.7, 6.2\text{Hz}$).

Reference Example 23

2-[5-methyl-2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethyl

methanesulfonate

IR ν (neat) cm^{-1} ; 2966, 2934, 2876, 1647, 1572, 1535.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.07 (3H, t, $J=6.8\text{Hz}$), 2.00 (3H, s), 2.05-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, $J=6.6\text{Hz}$), 2.94 (3H, s), 4.45 (2H, t, $J=6.6\text{Hz}$), 6.45 (1H, br-t).

Reference Example 24

2-[5-methyl-2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 3393, 2961, 2932, 2872, 1647, 1535.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.96 (3H, t, $J=7.0\text{Hz}$), 1.20-1.73 (2H, m), 2.00 (3H, s), 2.00-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, $J=6.6\text{Hz}$), 2.94 (1H, s), 4.45 (2H, t, $J=6.6\text{Hz}$), 6.46 (1H, dt, $J=1.4, 7.0\text{Hz}$).

Reference Example 25

2-[2-(trans-2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 2955, 2870, 1736, 1645, 1533.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.20-2.00 (8H, m), 2.26 (3H, s), 2.36-2.78 (1H, m), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.94 (3H, s), 4.44 (2H, t, $J=6.6\text{Hz}$), 6.14 (1H, d, $J=15.8\text{Hz}$), 6.62 (1H, dd, $J=15.8, 7.5\text{Hz}$).

Reference Example 26

2-(5-methyl-2-[2-trans-(1-methylcyclohexyl)vinyl]oxazol-4-yl)ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 2928, 2853, 1645, 1531, 1508.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.06 (3H, s), 1.20-1.80 (10H, m), 2.28 (3H, s), 2.87 (2H, t, $J=6.6\text{Hz}$), 2.95 (3H, s), 4.45 (2H, t, $J=6.6\text{Hz}$), 6.12 (1H, d, $J=16.5\text{Hz}$), 6.63 (1H, d, $J=16.3\text{Hz}$).

Reference Example 27

2-(5-methyl-2-[2-trans-(1-methylcyclopentyl)vinyl]oxazol-4-yl)ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 2957, 2872, 1645, 1551, 1533.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.15 (3H, s), 1.40-1.90 (8H, m), 2.27 (3H, s), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.94 (3H, s), 4.45 (2H, t,

J=6.6Hz), 6.13 (1H, d, J=16.3Hz), 6.71 (1H, d, J=16.3Hz).

Reference Example 28

2-[5-methyl-2-(2-methylsulfonyl)ethyl]oxazol-4-yl]ethyl methanesulfonate

⁵ IR ν (neat) cm⁻¹; 2922, 1651, 1576.

¹H-NMR (CDCl₃) δ (ppm); 2.12 (3H, s), 2.24 (3H, s), 2.60-3.20 (4H, m), 2.85 (2H, t, J=7.0Hz), 2.94 (3H, s), 4.43 (2H, t, J=7.0Hz).

Reference Example 29

¹⁰ **2-[2-(3,3-dimethyl-trans-1-buten-1-yl)-5-methyloxazol-4-yl]ethyl methanesulfonate**

IR ν (neat) cm⁻¹; 2962, 2907, 2869, 1660, 1645, 1532.

¹H-NMR (CDCl₃) δ (ppm); 1.11 (9H, s), 2.27 (3H, s), 2.86 (2H, t, J=6.6Hz), 2.94 (3H, s), 4.45 (2H, t, J=6.6Hz), 6.11 (1H, d,

¹⁵ J=16.2Hz), 6.67 (1H, d, J=16.2Hz).

Reference Example 30

2-[2-(4,4-dimethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm⁻¹; 2957, 2907, 2868, 1661, 1643, 1533.

²⁰ ¹H-NMR (CDCl₃) δ (ppm); 0.95 (9H, s), 2.10 (2H, d, J=7.5Hz), 2.28 (3H, s), 2.87 (2H, t, J=6.6Hz), 2.94 (3H, s), 4.45 (2H, t, J=6.6Hz), 6.15 (1H, d, J=16.0Hz), 6.65 (1H, dt, J=7.5, 16.0Hz).

Reference Example 31

2-[2-(3-ethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm⁻¹; 2963, 2928, 2876, 1643, 1578, 1551, 1533.

¹H-NMR (CDCl₃) δ (ppm); 0.86 (6H, t, J=6.8Hz), 1.20-1.70 (4H, m), 1.70-2.20 (1H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.6Hz), 2.94 (1H, s), 4.45 (2H, t, J=6.6Hz), 6.12 (1H, d, J=15.8Hz),

³⁰ 6.41 (1H, dd, J=15.8, 7.9Hz).

Reference Example 32

2-[2-(3,3-dimethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 3034, 3005, 1643, 1545.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.83 (3H, t, $J=7.4\text{Hz}$), 1.06 (6H, s),
1.43 (2H, q, $J=7.4\text{Hz}$), 2.27 (3H, s), 2.87 (2H, t, $J=6.7\text{Hz}$),
2.94 (1H, s), 4.45 (2H, t, $J=6.7\text{Hz}$), 6.09 (1H, d, $J=16.5\text{Hz}$),
5 6.59 (1H, d, $J=16.5\text{Hz}$).

Reference Example 33

2-(5-methyl-2-[(trans-2-thiophen-2-yl)vinyl]oxazol-4-yl)ethyl
methanesulfonate

IR ν (neat) cm^{-1} ; 3628, 3420, 3107, 3020, 2924, 1734, 1636,
10 1547.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.31 (3H, s), 2.90 (2H, t, $J=6.5\text{Hz}$),
2.95 (3H, s), 4.78 (2H, t, $J=6.5\text{Hz}$), 6.64 (1H, d, $J=16.1\text{Hz}$),
7.02 (1H, dd, $J=4.6, 3.2\text{Hz}$), 7.16 (1H, d, $J=3.2\text{Hz}$), 7.29 (1H, d,
 $J=4.6\text{Hz}$), 7.52 (1H, d, $J=16.1\text{Hz}$).

Reference Example 34

2-(5-methyl-2-phenylsulfanyloxazol-4-yl)ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 2928, 1507.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.25 (3H, s), 2.86 (2H, t, $J=6.5\text{Hz}$),
2.90 (3H, s), 4.44 (2H, t, $J=6.5\text{Hz}$), 7.30-7.75 (5H, m).

Reference Example 35

2-[2-(3-methoxy-trans-1-propen-1-yl)-5-methyloxazol-4-yl]ethyl
methanesulfonate

IR ν (neat) cm^{-1} ; 2930, 1354.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 2.28 (3H, s), 2.87 (2H, t, $J=6.4\text{Hz}$),
25 2.94 (3H, s), 3.39 (3H, s), 4.45 (2H, t, $J=6.5\text{Hz}$), 6.30-6.80
(2H, m).

Reference Example 36

2-[2-(5-fluoro-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethyl
methanesulfonate

30 IR ν (neat) cm^{-1} ; 2964, 2928, 2860, 1663, 1643, 1578, 1535.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 1.60-2.15 (2H, m), 2.20-2.50 (2H, m),
2.27 (3H, s), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.94 (3H, s), 4.45 (2H, t,
 $J=6.6\text{Hz}$), 4.49 (2H, dt, $J=5.8, 47.2\text{Hz}$), 6.21 (1H, d, $J=16.0\text{Hz}$),

6 63 (1H, dt, $J=16.0, 6.4\text{Hz}$).

Reference Example 37

2-[2-(2-cyclohexylidenemethyl)-5-methyloxazol-4-yl]ethyl methanesulfonate

⁵ IR ν (Nujol) cm^{-1} ; 1651, 1545, 1506.

¹H-NMR (CDCl_3) δ (ppm); 1.45-1.85 (6H, br), 2.10-2.45 (2H, br), 2.26 (3H, s), 2.65-3.00 (2H, br), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.93 (3H, s), 4.46 (2H, t, $J=6.6\text{Hz}$), 5.92 (1H, s).

Reference Example 38

¹⁰ 2-[2-(2-cyclopentylidenemethyl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 2957, 2870, 1659, 1645, 1576, 1545, 1526.

¹H-NMR (CDCl_3) δ (ppm); 1.50-2.00 (4H, m), 2.27 (3H, s), 2.30-3.00 (4H, m), 2.87 (2H, t, $J=6.6\text{Hz}$), 2.93 (3H, s), 4.46 (2H, t, $J=6.6\text{Hz}$), 6.10-6.25 (1H, m).

Reference Example 39

2-[2-(5-tert-butylsulfanyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 2961, 2928, 2862, 1641, 1578, 1535.

²⁰ ¹H-NMR (CDCl_3) δ (ppm); 1.32 (9H, s), 1.55-1.95 (2H, m), 2.15-2.40 (2H, m), 2.27 (3H, s), 2.57 (2H, t, $J=7.0\text{Hz}$), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.94 (3H, s), 4.44 (2H, t, $J=6.6\text{Hz}$), 6.18 (1H, d, $J=16.0\text{Hz}$), 6.61 (1H, dt, $J=16.0, 6.4\text{Hz}$).

Reference Example 40

²⁵ 2-[2-(5-dimethylamino-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethyl methanesulfonate

IR ν (neat) cm^{-1} ; 2941, 2862, 2818, 2775, 1643, 1533.

³⁰ ¹H-NMR (CDCl_3) δ (ppm); 1.40-1.90 (2H, m), 2.10-2.50 (4H, m), 2.22 (6H, s), 2.27 (3H, s), 2.86 (2H, t, $J=6.6\text{Hz}$), 2.94 (3H, s), 4.45 (2H, t, $J=6.6\text{Hz}$), 6.18 (1H, d, $J=16.1\text{Hz}$), 6.63 (1H, dt, $J=16.1, 6.4\text{Hz}$).

Reference Example 41

2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethyl

methanesulfonate

IR ν (neat) cm^{-1} ; 2959, 2930, 2872, 1661, 1597, 1549.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm); 0.95 (6H, d, $J=6.4\text{Hz}$), 1.50-2.00 (1H, m),
2.14 (2H, t, $J=6.8\text{Hz}$), 2.96 (3H, s), 2.96 (2H, t, $J=6.7\text{Hz}$),
5 4.48 (2H, t, $J=6.7\text{Hz}$), 6.21 (1H, d, $J=16.0\text{Hz}$), 6.70 (1H, dt,
 $J=16.0, 7.2\text{Hz}$), 7.40 (1H, s).

Experimental Example 1

Using male KK-A ^{y} mice, which were spontaneously diabetic
10 models, which had developed diabetes due to insulin resistance,
and which showed high plasma glucose, hypertriglyceridemia and
hyperinsulinemia, the pharmacological activity of the test
compounds was examined.

Test method

15 Blood was drawn under a non-fasting state from the tail
vein of male KK-A ^{y} mice, and the glucose and triglyceride
levels of the plasma were measured using commercially available
assay kits (glucose CII-test WAKO and triglyceride G-test WAKO,
Wako Pure Chemical Industries, Ltd.). The mice were grouped (5
20 mice per group) into a control group and an administration
group, such that the mean and standard deviation of the body
weight and the plasma glucose and plasma triglyceride levels in
each group were nearly the same. The test compounds (compounds
of Examples 1, 2, 4, 8, 20, 22, 24, 27, 30, 33, 36, 37, 40, 45,
25 47, 52, 56, 58 and 64) were suspended in 5% gum arabic solution
and administered (10 mg/kg/day) orally to the administration
group for 4 consecutive days. The 5% gum arabic solution was
orally administered to the control group. Blood was drawn
under a non-fasting state from the tail vein 24 hours after the
30 final administration and the glucose and triglyceride levels of
the plasma were measured. The decrease in the plasma glucose
and triglyceride levels was calculated from the following
formula. The results are shown in Table 1.

Decrease (%) = [(mean of control group - mean of test compound administration group) / mean of control group] X 100

5 Results

Table 1

Test compound	Decrease (%) in glucose level	Decrease (%) in triglyceride level
Example 1	46.1	45.3
Example 2	40.3	40.5
Example 4	40.3	40.5
Example 8	57.2	71.1
Example 20	57.7	65.6
Example 22	45.3	51.4
Example 24	52.8	50.7
Example 27	53.4	36.5
Example 30	55.4	57.0
Example 33	58.2	68.3
Example 36	39.8	27.5
Example 37	53.2	50.1
Example 40	54.3	37.0
Example 45	38.7	32.6
Example 47	29.9	10.9
Example 52	26.6	19.1
Example 56	21.0	11.9
Example 58	25.1	23.2
Example 64	29.4	25.1

Experimental, Example 2

Using db/db mice genetically showing high plasma glucose, hypertriglyceridemia, insulin resistance and obesity, the pharmacological activity of the test compounds of Examples 1, 2 and 20 was examined.

Test method

Blood was drawn under a non-fasting state from the tail vein of male db/db mice, the glucose level and triglyceride level of the plasma were measured using commercially available assay kits (glucose CII-test WAKO and triglyceride G-test WAKO, Wako Pure Chemical Industries, Ltd.). The mice were grouped (6

mice per group) into a control group and test compound (compounds of Examples 1, 2 and 20) administration group (3 mg/kg/day), such that the mean and standard deviation of the body weight and the plasma glucose and plasma triglyceride levels in each group were nearly the same. The test compound was suspended in 0.5% methylcellulose solution and administered orally for 2 consecutive weeks from the next day. The 0.5% methylcellulose solution was orally administered to the control group. Blood was drawn under a non-fasting state from the tail vein 24 hours after the final administration and the glucose and triglyceride levels of the plasma were measured. The decrease in the plasma glucose and triglyceride levels was calculated from the following formula. The results are shown in Table 2.

15

$$\text{Decrease (\%)} = [(\text{mean of control group} - \text{mean of test compound administration group}) / \text{mean of control group}] \times 100$$

Results

20

Table 2

Test compound	Decrease (%) in glucose level	Decrease (%) in triglyceride level
Example 1	21.3	62.7
Example 2	57.2	78.1
Example 20	54.0	72.0

Experimental Example 3

25

Using 7-week-old male ICR mice, toxicity by repeat administration was examined.

Test method

30

The mice were grouped (7 mice per group) into a control group and test compound (compounds of Examples 2 and 20) administration groups (30 and 100 mg/kg/day), such that the mean and the standard deviation of the body weight of the mice

were nearly the same. The test compound was suspended in 0.5% methylcellulose solution and administered orally for 2 consecutive weeks from the next day. The 0.5% methylcellulose solution was orally administered to the control group. At 24 hours after the final administration, Evans blue (100 µg/mouse) was administered from the tail vein and, 5 min later, the blood was drawn from the orbital venous plexus with anesthesia.

Using EDTA-added blood, hematocrit value and erythrocyte count were measured. Using the plasma, Evans blue concentration was measured, from which plasma volume was calculated. The liver and heart were removed and wet weight was measured.

Results

There was found no significant difference in the body weight, hematocrit value, erythrocyte count, plasma volume, weight of the liver and the heart of the test compound (compounds of Examples 2 and 20) administration (30 and 100 mg/kg/day) groups from those of the control group.

Experimental Example 4

Using 6-week-old female Wistar rats, toxicity by repeat administration was examined.

Test method

The rats were grouped (6 rats per group) into a control group and test compound (compounds of Examples 2 and 20) administration groups (30 and 100 mg/kg/day), such that the mean and the standard deviation of the body weight of the rats were nearly the same. The test compound was suspended in 0.5% methylcellulose solution and administered orally for 2 consecutive weeks from the next day. The 0.5% methylcellulose solution was orally administered to the control group. The rats were fasted for 16 hr from the last day of administration, anesthetized by intraperitoneal administration of pentobarbital sodium (50 mg/kg) 24 hr after the final administration and the

blood was drawn. Using EDTA-added blood, hematocrit value and erythrocyte count were measured, and using serum, AST (GOT) and ALT (GPT) were measured. In addition, the white fat around the uterus, and the liver and heart were removed and the wet weights thereof were measured.

Results

There was found no significant difference in the hematocrit value, erythrocyte count, weight of the white fat around the uterus, and the liver and heart, and AST (GOT) and ALT (GPT) of the test compound (compounds of Examples 2 and 20) administration (30 and 100 mg/kg/day) groups from those of the control group.

Experimental Example 5

The superior water-solubility of the compound of the present invention was confirmed by determining the solubility of the compound in water.

Test method

The pulverized test compound (compounds of Examples 2, 20, 22, 24, 27, 30, 40 or 65, 25 mg) was added to a buffer (1.0 ml, pH 7.0) and the mixture was shaken at 25°C for 1 hr and passed through a membrane filter. The concentration of the test compound in the filtrate was measured by high performance liquid chromatography. The results are shown in Table 3.

Results

Table 3

Test compound	Solubility (mg/ml)
Example 2	10.0
Example 20	25 or above
Example 22	25 or above
Example 24	18.7
Example 27	25 or above
Example 30	17.3
Example 40	18.7
Example 65	20.5

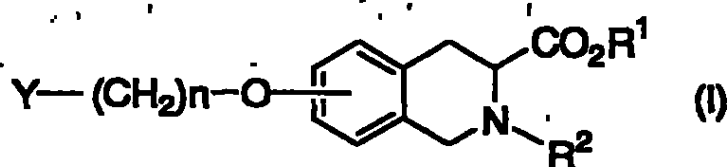
Industrial Applicability

5 The novel heterocyclic compound having the above-mentioned formula (I) of the present invention and a pharmaceutically acceptable salt thereof have a hypoglycemic action, a blood hypolipidemic action, an insulin resistance improving action and a PPAR activating action, and are useful
 10 as a hypoglycemic agent, a hypolipidemic agent, an insulin resistance improver, a therapeutic agent of diabetes, a therapeutic agent of diabetic complications, a glucose tolerance improver, an anti-arteriosclerosis agent, an anti-obesity agent, an antiinflammatory agent, an agent for the
 15 prophylaxis or treatment of PPAR-mediated diseases or an agent for the prophylaxis or treatment of syndrome X.

This application is based on patent application No. 2001-161489 filed in Japan, the contents of which are hereby
 20 incorporated by reference.

WHAT IS CLAIMED IS

1. A novel heterocyclic compound of the formula (I)



wherein

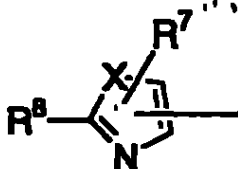
5 R¹ is a hydrogen atom or C₁₋₆ alkyl;

R² is a hydrogen atom, -CO-R³ wherein R³ is C₂₋₆ alkyl optionally substituted by halogen, -CO-C(R⁴)=C(R⁴)-R⁵ wherein R⁴ is optionally the same as the other R⁴ and is a hydrogen atom or C₁₋₄ alkyl, and R⁵ is C₁₋₈ alkyl, C₂₋₈ alkenyl, aryl or an aromatic heterocycle, -CO-C≡C-R⁶ wherein R⁶ is C₁₋₈ alkyl,



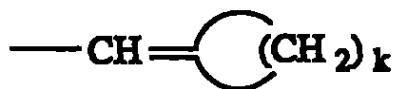
wherein m is an integer of 2 to 7, aryl, optionally substituted aryl C₁₋₃ alkyl, C₁₋₆ alkyl optionally substituted by halogen, C₂₋₆ alkenyl, C₃₋₈ cycloalkyl or C₃₋₈ cycloalkyl C₁₋₃ alkyl;

Y is



wherein R⁷ is a hydrogen atom or C₁₋₄ alkyl, R⁸ is C₃₋₈ alkyl, C₄₋₈ cycloalkyl, C₁₋₄ alkylthio C₁₋₆ alkyl, R¹⁰-C(R⁹)=C(R⁹)- wherein R⁹ is optionally the same as the other R⁹ and is a hydrogen atom or C₁₋₄ alkyl and R¹⁰ is C₁₋₆ alkyl optionally substituted by halogen, C₂₋₈ alkenyl, aryl, an aromatic heterocycle, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₃ alkyl, C₁₋₄ alkoxy C₁₋₆ alkyl, C₁₋₄ alkylthio C₁₋₆ alkyl or C₁₋₆ alkyl substituted by (R⁹)₂N- wherein R⁹

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is optionally the same as the other R⁹ and is a hydrogen atom or C₁₋₄ alkyl, R¹²-CO-N(R¹¹)- wherein R¹¹ is a hydrogen atom or C₁₋₄ alkyl and R¹² is C₁₋₆ alkyl or aryl, R¹³-Z- wherein R¹³ is C₁₋₆ alkyl or aryl and Z is an oxygen atom or a sulfur atom, or



wherein k is an integer of 2 to 7 and X is an oxygen atom or a sulfur atom, or

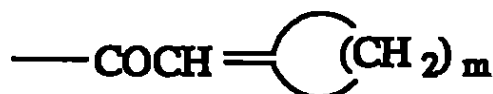
R¹⁵-C(R¹⁴)-N-O- wherein R¹⁴ is a hydrogen atom or C₁₋₄ alkyl and R¹⁵ is aryl or an aromatic heterocycle;

Y-(CH₂)_n-O- is bonded to the 6- or 7-position of a tetrahydroisoquinoline skeleton; and

n is an integer of 1 to 4

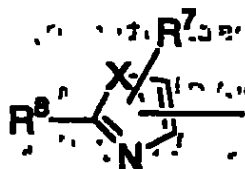
or a pharmaceutically acceptable salt thereof.

2. The novel heterocyclic compound of claim 1, wherein, in the formula (I), R² is an optionally substituted aryl C₁₋₃ alkyl, C₁₋₆ alkyl optionally substituted by halogen, C₂₋₆ alkenyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₃ alkyl or



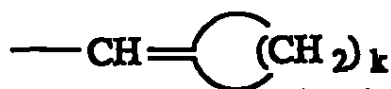
wherein m is an integer of 2 to 7, or a pharmaceutically acceptable salt thereof.

3. The novel heterocyclic compound of claim 1 wherein, in the formula (I), Y is



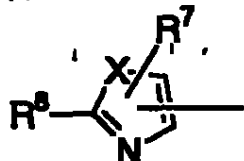
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wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is C_{1-4} alkylthio
 C_{1-6} alkyl, $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as
the other R^9 and is a hydrogen atom or C_{1-4} alkyl, R^{10} is C_{1-6}
alkyl optionally substituted by halogen, C_{3-8} cycloalkyl, C_{3-8}
cycloalkyl C_{1-3} alkyl, C_{1-4} alkoxy C_{1-6} alkyl, C_{1-4} alkylthio C_{1-6}
alkyl, C_{1-6} alkyl substituted by $(R^9)_2N-$ wherein R^9 is optionally
the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl,
or



wherein k is an integer of 2 to 7 and X is an oxygen atom or a
sulfur atom, or a pharmaceutically acceptable salt thereof.

4. The novel heterocyclic compound of claim 1 wherein, in the
formula (I), R^2 is a hydrogen atom, $-CO-R^3$ wherein R^3 is C_{2-6}
alkyl optionally substituted by halogen, $-COC(R^4)=C(R^4)-R^5$
wherein R^4 is optionally the same as the other R^4 and is a
hydrogen atom or C_{1-4} alkyl and R^5 is C_{1-8} alkyl, C_{2-8} alkenyl,
aryl or aromatic heterocycle, $-CO-C(R^6)=C(R^6)-R^6$ wherein R^6 is C_{1-8}
alkyl, or aryl, Y is



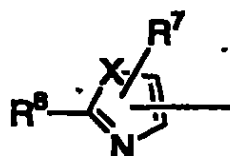
wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is C_{3-8} alkyl, C_{4-8}
cycloalkyl, $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same
as the other R^9 and is a hydrogen atom or C_{1-4} alkyl, R^{10} is C_{1-6}
alkyl, C_{2-8} alkenyl, aryl or an aromatic heterocycle, $R^{12}-CO-$
 $N(R^{11})-$ wherein R^{11} is a hydrogen atom or C_{1-4} alkyl, and R^{12} is
 C_{1-6} alkyl or aryl, or $R^{13}-Z-$ wherein R^{13} is C_{1-8} alkyl or aryl

and Z is an oxygen atom or a sulfur atom, and X is an oxygen atom or a sulfur atom, or $R^{15}-C(R^{14})=N-O-$ wherein R^{14} is a hydrogen atom or C_{1-4} alkyl and R^{15} is aryl or an aromatic heterocycle, or a pharmaceutically acceptable salt thereof.

5 5. The novel heterocyclic compound of claim 2 or 3, wherein, in the formula (I), $Y-(CH_2)_n-O-$ is bonded to the 7-position of a tetrahydroisoquinoline skeleton and n is 2, or a pharmaceutically acceptable salt thereof.

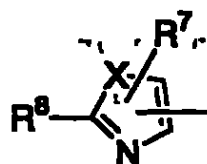
10 6. The novel heterocyclic compound of claim 4, wherein, in the formula (I), $Y-(CH_2)_n-O-$ is bonded to the 7-position of a tetrahydroisoquinoline skeleton and n is 2, or a pharmaceutically acceptable salt thereof.

15 7. The novel heterocyclic compound of claim 6 wherein, in the formula (I), Y is



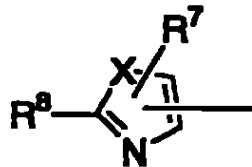
wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally, the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl, and R^{10} is C_{1-4} alkyl, C_{2-3} alkenyl or aryl, or a pharmaceutically acceptable salt thereof.

8. The novel heterocyclic compound of claim 6 wherein, in the formula (I), Y is



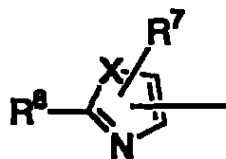
wherein R^7 is a hydrogen atom or C_{1-4} alkyl, R^8 is $R^{13}-Z-$ wherein R^{13} is C_{1-8} alkyl or aryl, and Z is a sulfur atom, or a pharmaceutically acceptable salt thereof. 135

9. The novel heterocyclic compound of claim 6 wherein, in the formula (I), Y is



- wherein R^7 is a hydrogen atom or C_{1-4} alkyl and R^8 is C_{3-8} alkyl or C_{4-8} cycloalkyl, or a pharmaceutically acceptable salt thereof.

10. The novel heterocyclic compound of claim 5 wherein, in the formula (I), Y is

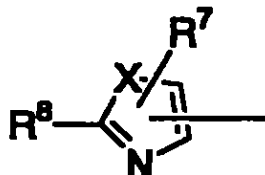


- wherein R^7 is a hydrogen atom or C_{1-4} alkyl and R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl and R^{10} is C_{3-8} cycloalkyl, or a pharmaceutically acceptable salt thereof.

11. The novel heterocyclic compound of any of claims 7 to 10, wherein, in the formula (I), R^2 is $-CO-C(R^4)=C(R^4)-R^5$ wherein R^4 is a hydrogen atom and R^5 is C_{1-8} alkyl or C_{2-8} alkenyl, or a pharmaceutically acceptable salt thereof.

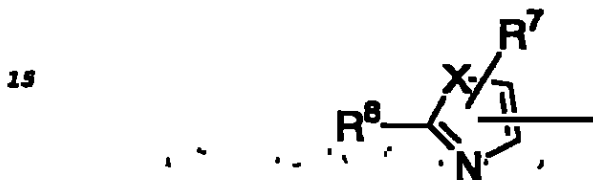
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12. The novel heterocyclic compound of any of claims 7 to 10, wherein, in the formula (I), R^2 is $-CO-C\equiv C-R^6$ wherein R^6 is C_{1-8} alkyl, or a pharmaceutically acceptable salt thereof.

13. The novel heterocyclic compound of any of claim 6, wherein, in the formula (I), Y is



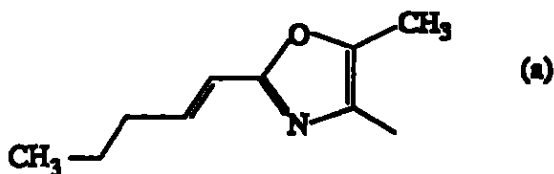
wherein R^7 is C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is optionally the same as the other R^9 and is a hydrogen atom or C_{1-4} alkyl and R^{10} is C_{1-6} alkyl, and X is an oxygen atom, or a pharmaceutically acceptable salt thereof.

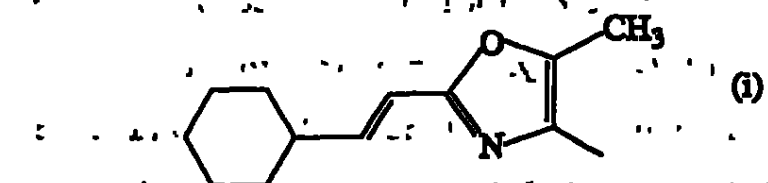
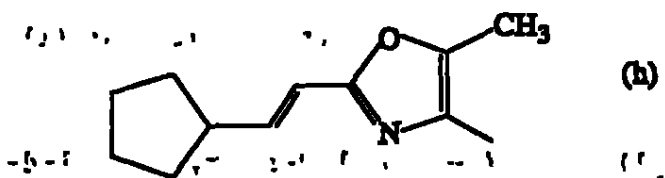
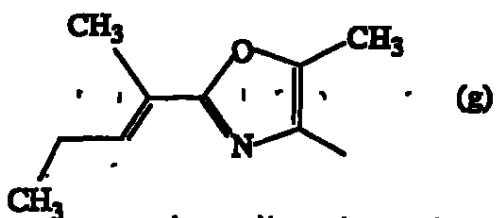
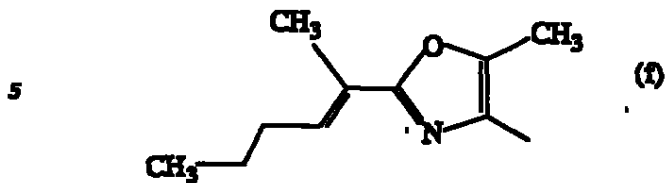
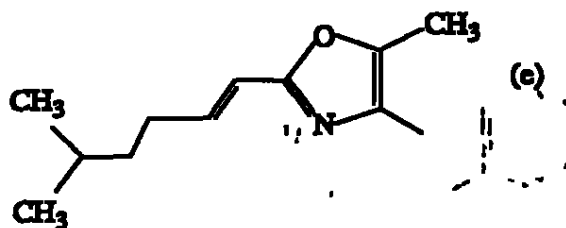
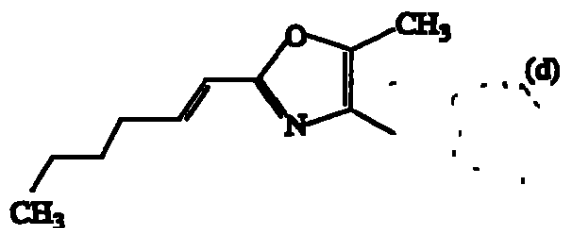
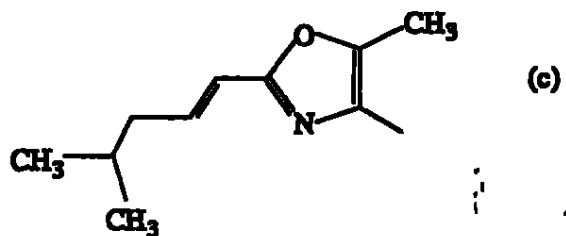
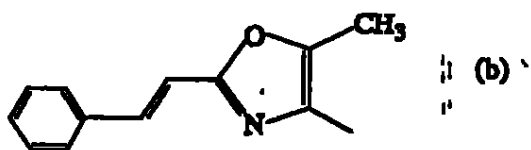
14. The novel heterocyclic compound of claim 6, wherein, in the formula (I), Y is

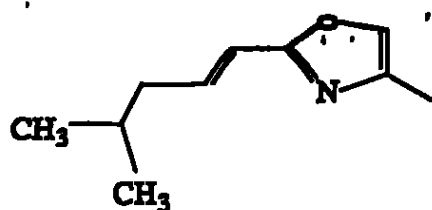


wherein R^7 is C_{1-4} alkyl, R^8 is $R^{10}-C(R^9)=C(R^9)-$ wherein R^9 is a hydrogen atom and R^{10} is aryl, and X is an oxygen atom, or a pharmaceutically acceptable salt thereof.

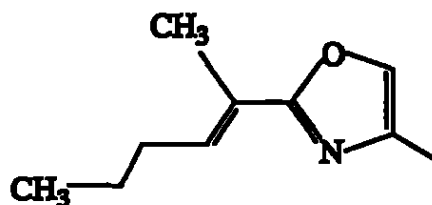
15. The novel heterocyclic compound of claim 4 or 5, wherein, in the formula (I), Y is selected from the following (a) to (n):



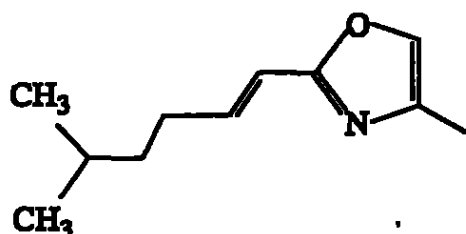




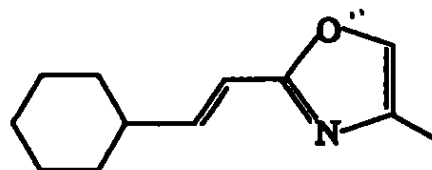
(j)



(k)



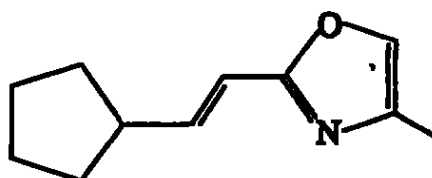
(l)



(m)

5

and



(n)

or a pharmaceutically acceptable salt thereof.

16. The novel heterocyclic compound of claim 1, wherein the
 10 compound of the formula (I) is any of the following (1) to
 (16):

- (1) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (2) 2-(2-heptenoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- 15 (3) 2-(2-hexynoyl)-7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-

- 1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, .
- (4) 7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-2-pentafluoropropionyl-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, .
- 5 (5) 2-(2-heptenoyl)-7-[2-(5-methyl-2-styrylthiazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- 6 (6) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- 10 (7) 2-(2-heptenoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (8) 2-(2-hexynoyl)-7-[2-(5-methyl-2-(1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (9) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(1,3-pentadien-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- 15 (10) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-pentyloxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (11) 7-[2-(2-cyclopentyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- 20 (12) 7-[2-(2-cyclohexyl-5-methyloxazol-4-yl)ethoxy]-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- 25 (13) 7-[2-(2-benzoylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (14) 7-[2-(2-butyrylaminothiazol-5-yl)ethoxy]-2-(2-heptenoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- (15) 2-(2-heptenoyl)-7-[2-(4-methyl-2-phenylsulfanylthiazol-5-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,
- 30

and

(16) 2-(2-heptenoyl)-7-[2-(1-phenylethylideneaminoxy)ethoxy]-1,2,3,4-tetrahydr isoquinoline-(3S)-carboxylic acid,
or a pharmaceutically acceptable salt thereof.

5

17. The novel heterocyclic compound of claim 1, wherein the compound of the formula (I) is any of the following (1) to (3):

(1) 7-[2-(5-methyl-2-styryloxazol-4-yl)ethoxy]-2-pentafluoropropionyl-1,2,3,4-tetrahydroisoquinoline-(3S)-
10 carboxylic acid,

(2) 2-(2-heptenoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and

(3) 2-(2-hexynoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-
15 carboxylic acid,

or a pharmaceutically acceptable salt thereof.

18. The novel heterocyclic compound of claim 1, wherein the
20 compound of the formula (I) is any of the following (1) to (17):

(1) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

25 (2) 2-(2-heptenoyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(3) 2-(2,4-hexadienoyl)-7-{2-[2-(1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic
30 acid,

(4) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(5-methyl-1-hexen-1-

- yl)oxazol-4-yl]ethoxy)-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (5) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-1-penten-1-
yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
5 carboxylic acid,
- (6) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-1-buten-1-
yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (7) 2-(2-hexenoyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-
10 yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (8) 7-{2-[5-methyl-2-(1-penten-1-yl)oxazol-4-yl]ethoxy}-2-
(2,2,3,3,3-pentafluoropropionyl)-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylic acid,
- 15 (9) 7-{2-[2-(4,4-dimethyl-1-penten-1-yl)-5-methyloxazol-4-
yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid,
- (10) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(3-methyl-1-buten-1-
yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
20 carboxylic acid,,
- (11) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-[2-(1-
methylcyclohexan-1-yl)vinyl]oxazol-4-yl]ethoxy}-1,2,3,4-
tetrahydroisoquinoline-(3S)-carboxylic acid,
- (12) 7-{2-[2-(3,3-dimethyl-1-buten-1-yl)-5-methyloxazol-4-
25 yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid,
- (13) 2-(2,4-hexadienoyl)-7-{2-[2-(3-methoxy-1-propen-1-yl)-5-
methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- 30 (14) 7-{2-[2-(2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy}-
2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,
- (15) 7-{2-[2-(2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-

(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,

(16) 2-(3-butenyl)-7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
5 carboxylic acid, and

(17) 7-{2-[5-methyl-2-(4-methyl-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,

or a pharmaceutically acceptable salt thereof.

- 10

19. The novel heterocyclic compound of claim 1, wherein the
compound of the formula (I) is any of the following (1) to (8):

(1) 2-(2,4-hexadienoyl)-7-[2-(5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydroisoquinoline-(3S)-
15 carboxylic acid,

(2) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid,

(3) 2-(2-heptenoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
20 carboxylic acid,

(4) 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-
carboxylic acid,

(5) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-
(3S)-carboxylic acid,

(6) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-

30 (3S)-carboxylic acid, and

(7) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid, and

(8) 2-(2-hexenoyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

20. The novel heterocyclic compound of claim 1, wherein the compound of the formula (I) is any of the following (1) to (6):

(1) 7-{2-[5-methyl-2-(trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(2,2,3,3,3-pentafluoropropionyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(2) 7-{2-[2-(4,4-dimethyl-trans-1-penten-1-yl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylic acid,

(3) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-(3-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(4) 2-(2,4-hexadienoyl)-7-{2-[5-methyl-2-[2-trans-(1-methylcyclohexan-1-yl)vinyl]oxazol-4-yl]ethoxy}-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylic acid,

(5) 7-{2-[2-(3,3-dimethyl-trans-1-buten-1-yl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-

tetrahydroisoquinoline-(3S)-carboxylic acid, and

(6) 2-(2,4-hexadienoyl)-7-{2-[2-(3-methoxy-trans-1-propen-1-yl)-5-methyloxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

30

21. The novel heterocyclic compound of claim 1, wherein the compound of the formula (I) is the following (1) or (2):

(1) 7-{2-[2-(trans-2-cyclopentylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-

5 (3S)-carboxylic acid,

(2) 7-{2-[2-(trans-2-cyclohexylvinyl)-5-methyloxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-

(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

10

22. The novel heterocyclic compound of claim 1, wherein the compound of the formula (I) is the following (1) or (2):

(1) 2-(3-butenyl)-7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-

15 carboxylic acid,

(2) 7-{2-[5-methyl-2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-2-(4-pentenyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

20

23. The novel heterocyclic compound of claim 1, wherein the compound of the formula (I) is any of the following (1) to (9):

(1) 2-(2,4-hexadienoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-

25 carboxylic acid,

(2) 7-{2-[2-(trans-2-cyclopentylvinyl)oxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(3) 7-{2-[2-(trans-2-cyclohexylvinyl)oxazol-4-yl]ethoxy}-2-(2,4-hexadienoyl)-1,2,3,4-tetrahydroisoquinoline-(3S)-

30

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carboxylic acid,

(4) 2-(2-heptenoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

5 (5) 2-(2-hexenoyl)-7-{2-[2-(4-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(6) 2-(2,4-hexadienoyl)-7-{2-[2-(trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

10 (7) 2-(2,4-hexadienoyl)-7-{2-[2-(1-methyl-trans-1-penten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

(8) 2-(2,4-hexadienoyl)-7-{2-[2-(1-methyl-trans-1-buten-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-

15 carboxylic acid, and

(9) 2-(2,4-hexadienoyl)-7-{2-[2-(5-methyl-trans-1-hexen-1-yl)oxazol-4-yl]ethoxy}-1,2,3,4-tetrahydroisoquinoline-(3S)-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

20

24. A pharmaceutical composition containing the novel heterocyclic compound of any of claims 1 to 23, or a pharmaceutically acceptable salt thereof.

25 25. A pharmaceutical agent containing the novel heterocyclic compound of any of claims 1 to 23, or a pharmaceutically acceptable salt thereof, which agent is selected from the group consisting of a hypoglycemic agent, a hypolipidemic agent, an insulin resistance improver, a therapeutic agent of diabetes, a
30 therapeutic agent of diabetic complications, a glucose tolerance improver, an anti-arteriosclerosis agent, an anti-obesity agent, an antiinflammatory agent, an agent for the prophylaxis or treatment of PPAR-mediated diseases and an agent

for the prophylaxis or treatment of syndrome X.

26. A method for the prophylaxis or treatment of diabetes,
diabetic complication, hyperlipidemia, arteriosclerosis,
5 hyperglycemia, diseases caused by insulin resistance glucose
intolerance, diseases caused by insulin resistance, obesity,
inflammation, PPAR-mediated disease or syndrome X, which
comprises administering a pharmaceutically effective amount of
the heterocyclic compound of any of claims 1 to 23 or a
10 pharmaceutically acceptable salt thereof to a patient.

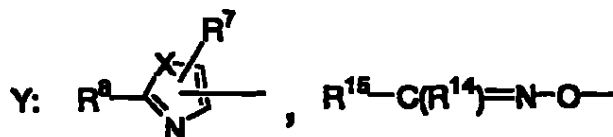
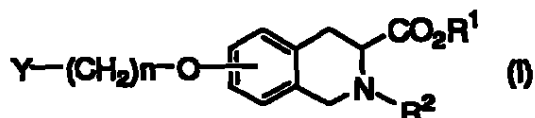
27. Use of a novel heterocyclic compound of any of claims 1 to
23 or a pharmaceutically acceptable salt thereof for the
production of a pharmaceutical composition for the prophylaxis
15 or treatment of diabetes, diabetic complication, hyperlipidemia,
arteriosclerosis, hyperglycemia, diseases caused by insulin
resistance glucose intolerance, diseases caused by insulin
resistance, obesity, inflammation, PPAR-mediated disease or
syndrome X.

20

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Abstract

The novel heterocyclic compound of the present invention is a novel heterocyclic compound having the formula (I)



wherein R¹ is H or C₁₋₆ alkyl, R² is H, -CO-C(R⁴)=C(R⁴)-R⁵ wherein R⁴ is H or C₁₋₄ alkyl, and R⁵ is C₄₋₆ alkyl, C₂₋₆ alkenyl and the like, and the like, Y is the following group wherein X is O or S, R⁷ is the same as R⁴, R⁸ is R¹⁰-C(R⁹)=C(R⁹)- wherein R⁹ is the same as R⁴, R¹⁰ is C₃₋₆ alkyl and the like, and the like, R¹⁴ is the same as R⁴, and R¹⁵ is aryl and the like, Y-(CH₂)_n-O- is bonded to the 6- or 7-position of the tetrahydroisoquinoline skeleton, and n is an integer of 1 to 4, or a pharmaceutically acceptable salt thereof. The compound (I) of the present invention is useful as a hypoglycemic agent, a hypolipidemic agent, an insulin resistance improver, a therapeutic agent of diabetes, a therapeutic agent of diabetic complications, a glucose tolerance improver, an anti-arteriosclerosis agent, an anti-obesity agent, an antiinflammatory agent, an agent for the prophylaxis or treatment of PPAR-mediated diseases or an agent for the prophylaxis or treatment of syndrome X.

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Nuevas compuestas heterocíclicas y uso farmacológico de los mismos

Cuerpo técnico de la Inspección

La presente invención se refiere a un nuevo compuesto heterocíclico y una sal farmacéuticamente aceptable del mismo, al cual tiene una acción hipoglucémica, una acción hipolipídica en sangre, una acción mejoradora de la resistencia a la insulina y una acción que active el PPAR (receptor activado por el proliferador de peroxisoma). La presente invención también se refiere a una composición farmacéutica que comprende el nuevo derivado heterocíclico recién mencionado o una sal farmacéuticamente aceptable del mismo. Por otra parte la presente invención se refiere a un agente hipoglucémico, un agente hipolipídico, un mejorador de la resistencia a la insulina, un agente terapéutico de diabetes, un agente terapéutico de complicaciones diabéticas, un mejorador de la tolerancia a la glucosa, un agente antiarterioesclerosis, un agente antiobesidad, un agente antiinflamatorio, un agente para la profilaxis o tratamiento de enfermedades mediadas por el PPAR y un agente para la profilaxis o el tratamiento del síndrome X, los cuales comprenden todos el nuevo compuesto

insulina Como agente que mejora la resistencia a la insulina se conocen varios compuestos de tiavelidina Los ejemplos de ese compuesto incluyen 5-[4-[(6-hidroxi-2,5,7,8-tetrametilcristman-2-il)metoxi]bencil]-2,4-tiavelidindiona (nombre general troglitazona); se describe en la USP 4572912 y EP013942131. 3-[[4-(2-13-etil-piridin-2-il)etoxi]fenil]metil]-2,4-tiavelidindiona (nombre general, troglitazona) se describe en la USP4667777 y EP019323621, y 5-[[4-(2-N-metil-N-(piridin-2-il)amino]etoxi]fenil]metil]-2,4-tiavelidindiona (nombre general rasiglitazona) se describe en la USP3602953 y EP030627851 Sin embargo, estos agentes farmacuticos que mejoran la resistencia a la insulina pueden causar efectos colaterales como hepatopatia, retención de liquidos, edema, miocardiopatia, obesidad y similares De esta manera se desea el desarrollo de un mejorador de la resistencia a la insulina altamente seguro que sea efectivo para la NIDDM

Resumen de la invención

Por lo tanto, es un objeto de la presente invención prever un compuesto que tenga una acción hipoglucémica, una acción hipolipidémica en sangre una acción mejoradora de la resistencia a la insulina y una acción activadora del FFAA, que tiene una estructura completamente diferente a la de los compuestos convencionales y que es altamente segura.

heterociclico mencionado o una sal farmacuticamente
aceptable del mismo

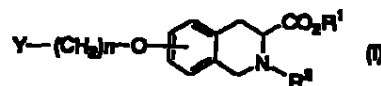
Aplicaciones de la inversión

Como agente terapéutica de la diabetes, se conocen compuestos de biguanida que tienen como acción principal una acción inhibidora sobre la absorción de la glucosa a través del tracto intestinal y sobre la liberación de la glucosa proveniente del hígado, compuestos de sulfonilurea que tienen una acción aceleradora sobre la secreción de insulina como acción principal, insulina y similares. Sin embargo, los compuestos de biguanida causan acidosis láctica y los compuestos de sulfonilurea causan a veces hipoglucemia severa debido a su fuerte acción hipoglucémica. En consecuencia, debe tenerse suficiente cuidado cuando se usan estos compuestos. En los últimos años, hubo investigaciones y desarrollos activos de un agente terapéutico de la diabetes que no adolece de estos defectos, con la consecuencia de haber hallado varios compuestos que tienen una acción que mejora la resistencia a la insulina.

La resistencia a la insulina juega un papel importante como causa de la diabetes mellitus no dependiente de la insulina (NIDDM), junto con la reducción de la secreción de

para incrementar la diversidad en y para ampliar el rango de selección de los agentes hipoglucémicos, agentes hipolipidémicos, mejoradores de la resistencia a la insulina, agentes terapéuticos de la diabetes, agentes terapéuticos de complicaciones diabéticas, mejoradores de la tolerancia a la glucosa, agentes antiarterioesclerosis, agentes antiobesidad, agentes antiinflamatorios, agentes para la profilaxis o el tratamiento de enfermedades mediadas por el PPAR y agentes para la profilaxis o el tratamiento del síndrome X.

Los presentes inventores realizaron vastos estudios en un intento por solucionar los problemas antes mencionados y hallaron que un azarce compuesto heterociclico de la fórmula (I'):

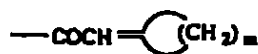


• • •

R^1 es un átomo de hidrógeno o alquilo C_{1-4}

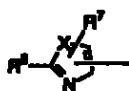
R¹ es un átomo de hidrógeno, -CO-R¹, donde R¹ es alquilo
o, opcionalmente, sustituido por halógeno, -CO-

$C(R^1)-C(R^1)-R^2$, donde R^1 es opcionalmente el mismo que el otro R^1 y es un átomo de hidrógeno o alquilo C_{1-4} , y R^2 es alquilo C_{1-4} , alquenilo C_{2-4} , arilo o heterociclo aromático, $-CO-C-C-R^3$, donde R^3 es alquilo C_{1-4} .



donde m es un número entero de 2 a 7, arilo, arilalquilo C_1 , opcionalmente sustituido, alquilo C_{1-4} , opcionalmente sustituido por halógeno, alquenilo C_{2-4} , cicloalquilo C_{3-4} o cicloalquil C_{3-4} -alquilo C_{1-4} .

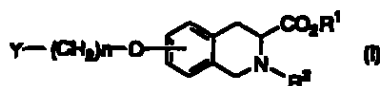
Y es



donde R^7 es un átomo de hidrógeno o alquilo C_{1-4} , R^8 es alquilo C_{1-4} , cicloalquilo C_{3-4} , alquiltil C_{1-4} -alquilo C_{1-4} , $R^{10}-C(R^9)-C(R^9)-$, donde R^9 es opcionalmente el mismo que el otro R^9 y es un átomo de hidrógeno o alquilo C_{1-4} y R^{10} es alquilo C_{1-4} opcionalmente sustituido por halógeno, alquenilo C_{2-4} , arilo, un heterociclo aromático, cicloalquilo C_{3-4} , cicloalquil C_{3-4} -alquilo C_{1-4} , alcoxí C_{1-4} -alquilo C_{1-4} , alquiltil C_{1-4} .

De acuerdo con ello, la presente invención provee lo siguiente

(1) Un nuevo compuesto heterocíclico de la fórmula (I)



donde

R^1 es un átomo de hidrógeno o alquilo C_{1-4} .

R^2 es un átomo de hidrógeno, $-CO-R^3$, donde R^3 es alquilo C_{1-4} opcionalmente sustituido por halógeno, $-CO-C(R^1)-C(R^1)-R^4$, donde R^1 es opcionalmente el mismo que el otro R^1 y es un átomo de hidrógeno o alquilo C_{1-4} , y R^4 es alquilo C_{1-4} , alquenilo C_{2-4} , arilo o un heterociclo aromático, $-CO-C-C-R^5$, donde R^5 es alquilo C_{1-4} .



donde m es un número entero de 2 a 7, arilo, arilalquilo C_1 , opcionalmente sustituido, alquilo C_{1-4} .

o alquilo C_{1-4} o alquilo C_{1-4} sustituido por $(R^6)_2N-$, donde R^6 es opcionalmente el mismo que el otro R^6 y es un átomo de hidrógeno o alquilo C_{1-4} , $R^{11}-CO-N(R^{11})-$, donde R^{11} es un átomo de hidrógeno o alquilo C_{1-4} , y R^{12} es alquilo C_{1-4} o arilo, $R^{12}-S-$, donde R^{12} es alquilo C_{1-4} , o arilo y S es un átomo de oxígeno o un átomo de azufre, o



donde k es un número entero de 2 a 7 y X es un átomo de oxígeno o un átomo de azufre, o

$R^{13}-C(R^{14})-N-O-$, donde R^{14} es un átomo de hidrógeno o alquilo C_{1-4} y R^{13} es arilo o un heterociclo aromático;

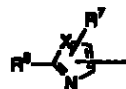
$Y-(CH_2)_n-O-$ está unido a la posición 4 ó 7 de un esqueleto de tetrahidroquinolina; y

n es un número entero de 1 a 4

y una sal farmacológicamente aceptable de los mismos tienen una acción hipotenciva, una acción hipolipídica en sangre, una acción mejoradora de la resistencia a la insulina y una acción que active el PPAR así como una elevada seguridad

opcionalmente sustituido por halógeno, alquenilo C_{2-4} , cicloalquilo C_{3-4} o cicloalquil C_{3-4} -alquilo C_{1-4} .

Y es



donde R^7 es un átomo de hidrógeno o alquilo C_{1-4} , R^8 es alquilo C_{1-4} , cicloalquilo C_{3-4} , alquiltil C_{1-4} -alquilo C_{1-4} , $R^{10}-C(R^9)-C(R^9)-$, donde R^9 es opcionalmente el mismo que el otro R^9 y es un átomo de hidrógeno o alquilo C_{1-4} y R^{10} es alquilo C_{1-4} opcionalmente sustituido por halógeno, alquenilo C_{2-4} , arilo o un heterociclo aromático, cicloalquilo C_{3-4} , cicloalquil C_{3-4} -alquilo C_{1-4} , alcoxí C_{1-4} -alquilo C_{1-4} , alquiltil C_{1-4} -alquilo C_{1-4} o alquilo C_{1-4} sustituido por $(R^6)_2N-$, donde R^6 es opcionalmente el mismo que el otro R^6 y es un átomo de hidrógeno o alquilo C_{1-4} , $R^{11}-CO-N(R^{11})-$, donde R^{11} es un átomo de hidrógeno o alquilo C_{1-4} y R^{12} es alquilo C_{1-4} o arilo, $R^{12}-S-$, donde R^{12} es alquilo C_{1-4} , o arilo y S es un átomo de oxígeno o un átomo de azufre, o



donde k es un número entero de 2 a 7 y X es un átomo de oxígeno o un átomo de azufre, o

$R^{1b}-C(R^{1c})=N-O-$, donde R^{1c} es un átomo de hidrógeno o alquilo C_{1-4} y R^{1b} es arilo o un heterociclo aromático;

$Y-(CH_2)_n-O-$ está enlazado a la posición 6 ó 7 de un esqueleto de tetrahidroisoquinolina; y

n es un número entero de 1 a 4,

o una sal farmacéuticamente aceptable de los mismos

[2] El nuevo compuesto heterocíclico del punto anterior [1], donde, en la fórmula (I), R^1 es un arilalquilo C_{1-3} opcionalmente sustituido, alquilo C_{1-4} opcionalmente sustituido por halógeno, alquenilo C_{2-4} , cicloalquilo C_{3-4} , cicloalquil C_{3-4} -alquilo C_{1-3} o

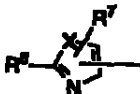


donde m es un número entero de 2 a 7, o una sal farmacéuticamente aceptable de los mismos.

[3] El nuevo compuesto heterocíclico del punto anterior [1], donde, en la fórmula (I), Y es

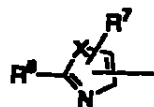
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hidrógeno o alquilo C_{1-4} y R^1 es alquilo C_{1-4} , alquenilo C_{2-4} , arilo o heterociclo aromático $-CO-C\equiv C-R^2$, donde R^2 es alquilo C_{1-4} , o arilo, y es



donde R^1 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es alquilo C_{1-4} , cicloalquilo C_{3-4} , $R^{1b}-C(R^{1c})-C(R^{1d})-$, donde R^{1b} es opcionalmente el mismo que el otro R^{1c} y es un átomo de hidrógeno o alquilo C_{1-4} , R^{1d} es alquilo C_{1-4} , alquenilo C_{2-4} , arilo o heterociclo aromático, $R^{1b}-CO-N(R^{1e})-$, donde R^{1e} es un átomo de hidrógeno o alquilo C_{1-4} , y R^{1d} es alquilo C_{1-4} o arilo, o $R^{1b}-Z-$, donde R^{1b} es alquilo C_{1-4} o arilo y Z es un átomo de oxígeno o un átomo de azufre, y X es un átomo de oxígeno o un átomo de azufre, o $R^{1b}-C(R^{1c})=N-O-$, donde R^{1c} es un átomo de hidrógeno o alquilo C_{1-4} y R^{1b} es arilo o heterociclo aromático, o una sal farmacéuticamente aceptable de los mismos

[5] El nuevo compuesto heterocíclico de los puntos anteriores [2] o [3], donde, en la fórmula (I), $Y-(CH_2)_n-O-$ está enlazado con la posición 7 del esqueleto de una tetrahidroisoquinolina y n es 2, o una sal farmacéuticamente aceptable de los mismos



donde R^1 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es alquililil C_{1-4} -alquilo C_{1-4} , $R^{1b}-C(R^{1c})-C(R^{1d})-$, donde R^{1b} es opcionalmente el mismo que el otro R^{1c} y es un átomo de hidrógeno o alquilo C_{1-4} , R^{1d} es alquilo C_{1-4} opcionalmente sustituido por halógeno, cicloalquilo C_{3-4} , cicloalquil C_{3-4} -alquilo C_{1-4} , alcoli C_{1-4} -alquilo C_{1-4} , alquililil C_{1-4} -alquilo C_{1-4} , alquilo C_{1-4} sustituido por $(R^{1e})_m$, donde R^{1e} es opcionalmente el mismo que el otro R^{1e} y es un átomo de hidrógeno o alquilo C_{1-4} , o



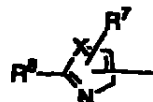
donde k es un número entero de 2 a 7, y X es un átomo de oxígeno o un átomo de azufre o una sal farmacéuticamente aceptable de los mismos

[4] El nuevo compuesto heterocíclico del punto anterior [1], donde, en la fórmula (I), R^1 es un átomo de hidrógeno, $-CO-R^2$, donde R^2 es alquilo C_{1-4} opcionalmente sustituido por halógeno, $-CO-C(R^3)-C(R^4)-R^5$, donde R^3 es opcionalmente el mismo que el otro R^4 y es un átomo de

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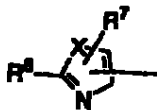
[6] El nuevo compuesto heterocíclico del punto anterior [4] donde, en la fórmula (I), $Y-(CH_2)_n-O-$ está enlazado con la posición 7 del esqueleto de una tetrahidroisoquinolina y n es 2, o una sal farmacéuticamente aceptable de los mismos

[7] El nuevo compuesto heterocíclico del punto anterior [5], donde, en la fórmula (I) Y es



donde R^1 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es $R^{1b}-C(R^{1c})-C(R^{1d})-$, donde R^{1b} es opcionalmente el mismo que el otro R^{1c} y es un átomo de hidrógeno o alquilo C_{1-4} y R^{1d} es alquilo C_{1-4} , alquenilo C_{2-4} , o arilo, o una sal farmacéuticamente aceptable de los mismos

[8] El nuevo compuesto heterocíclico del punto anterior [6], donde, en la fórmula (I), Y es



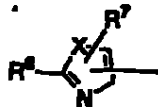
donde R^6 es un átomo de hidrógeno o alquilo C_{1-4} , R^7 es R^{11} - E -, donde R^{11} es alquilo C_{1-4} o arilo, y E es un átomo de azufre o una sal farmacéuticamente aceptable de los mismos

[9] El nuevo compuesto heterocíclico del punto anterior [6], donde, en la fórmula (I), Y es



donde R^6 es un átomo de hidrógeno o alquilo C_{1-4} y R^7 es alquilo C_{1-4} o cicloalquilo C_{3-6} , o una sal farmacéuticamente aceptable de los mismos

[10] El nuevo compuesto heterocíclico del punto anterior [3], donde, en la fórmula (I), Y es

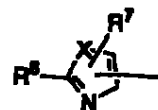


donde R^6 es alquilo C_{1-4} , R^7 es $R^{12}-C(R^3)-C(R^3)-$, donde R^3 es opcionalmente el mismo que el otro R^3 y es un átomo de hidrógeno o alquilo C_{1-4} y R^{12} es alquilo C_{1-4} y X es un átomo de oxígeno, o una sal farmacéuticamente aceptable de los mismos

[14] El nuevo compuesto heterocíclico del punto anterior [6], donde, en la fórmula (I), Y es



donde R^6 es alquilo C_{1-4} , R^7 es $R^{14}-C(R^4)-C(R^4)-$, donde R^4 es un átomo de hidrógeno y R^{14} es arilo, y X es un átomo de oxígeno, o una sal farmacéuticamente aceptable de los mismos



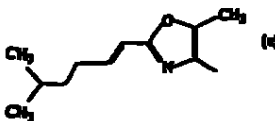
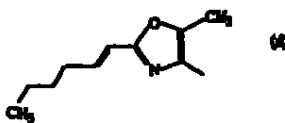
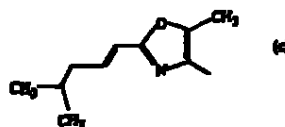
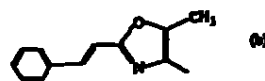
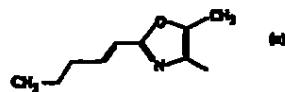
donde R^6 es un átomo de hidrógeno o alquilo C_{1-4} y R^7 es $R^{15}-C(R^5)-C(R^5)-$, donde R^5 es opcionalmente el mismo que el otro R^5 y es un átomo de hidrógeno o alquilo C_{1-4} y R^{15} es cicloalquilo C_{3-6} , o una sal farmacéuticamente aceptable de los mismos

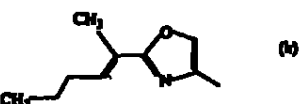
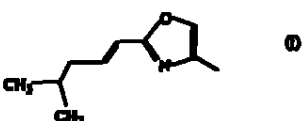
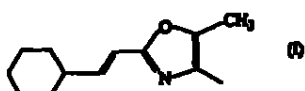
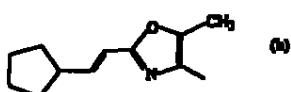
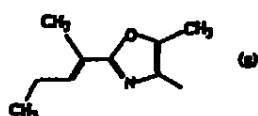
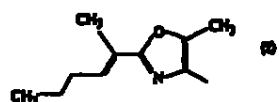
[11] El nuevo compuesto heterocíclico de cualquiera de los puntos anteriores [7] a [10], donde, en la fórmula (I), R^6 es $-CO-C(R^6)-C(R^6)-R^6$, donde R^6 es un átomo de hidrógeno y R^7 es alquilo C_{1-4} o alquilarilo C_{1-6} , o una sal farmacéuticamente aceptable de los mismos

[12] El nuevo compuesto heterocíclico de cualquiera de los puntos anteriores [7] a [10] anteriores, donde en la fórmula (I), R^6 es $-CO-C-C-R^6$ donde R^6 es alquilo C_{1-4} , o una sal farmacéuticamente aceptable de los mismos

[13] El nuevo compuesto heterocíclico del punto anterior [8], donde, en la fórmula (I), Y es

[15] El nuevo compuesto heterocíclico de los puntos anteriores [4] o [5], donde, en la fórmula (I), Y está seleccionado de los siguientes (a) a (n)





(3) Ácido 2-(2-hexenoil)-7-[2-(3-metil-2-estiriloxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

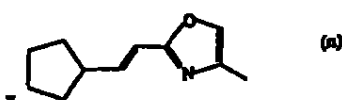
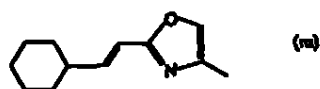
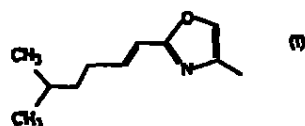
(4) Ácido 7-[2-(3-metil-2-estiriloxazol-4-il)etoxi]-2-pentafluoropropionil-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(5) Ácido 2-(2-heptenoil)-7-[2-(3-metil-2-estiriloxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(6) Ácido 2-(2,4-hexadienoil)-7-[2-(3-metil-2-(1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(7) Ácido 2-(2-heptenoil)-7-[2-(3-metil-2-(1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(8) Ácido 2-(2-hexenoil)-7-[2-(3-metil-2-(1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,



o sea en farmacológicamente aceptable de las mismas

(16) El nuevo compuesto heterocíclico del punto anterior (1), desde el compuesto de la fórmula (1) es cualquiera de los siguientes (1) a (16)

(1) Ácido 2-(2,4-hexadienoil)-7-[2-(3-metil-2-estiriloxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

(2) Ácido 2-(2-heptenoil)-7-[2-(3-metil-2-estiriloxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(9) Ácido 2-(2,4-hexadienoil)-7-[2-(3-metil-2-(1,3-pentadien-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

(10) Ácido 2-(2,4-hexadienoil)-7-[2-(3-metil-2-pentiloxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

(11) Ácido 7-[2-(2-ciclopentil-5-metiloxazol-4-il)etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(12) Ácido 7-[2-(2-ciclohexil-5-metiloxazol-4-il)etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

(13) Ácido 7-[2-(2-benzilaminotiazol-5-il)etoxi]-2-(2-heptenoil)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(14) Ácido 7-[2-(2-butilaminotiazol-5-il)etoxi]-2-(2-heptenoil)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico,

(15) Ácido 2-(2-heptenoil)-7-(2-(4-metil-2-fenilsulfamiltiazol-5-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico, y

(16) Ácido 2-(2-heptenoil)-7-(2-(1-feniltiolidanaminometil)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

o una sal farmacéuticamente aceptable de los mismos

(17) El nuevo compuesto heterocíclico del punto anterior (1), donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (3):

(1) Ácido 7-(2-(3-metil-2-estiriloxazol-4-il)etoxi)-3-pentafluoropropionil-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(2) Ácido 2-(2-heptenoil)-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico, y

(3) Ácido 2-(2-hexenoil)-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(5) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(1-metil-1-buten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(7) Ácido 2-(2-hexenoil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(8) Ácido 7-(2-(5-metil-2-(1-penten-1-il)oxazol-4-il)etoxi)-2-(2,2,3,3,3-pentafluoropropionil)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(9) Ácido 7-(2-(2-(4,4-dimetil-1-penten-1-il)-5-metiloxazol-4-il)etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(10) Ácido 2-(2,4-hexadienoil)-7-(2-(3-metil-2-(3-metil-1-buten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(11) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(2-(1-metilciclohexan-1-il)vinil)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

o una sal farmacéuticamente aceptable de los mismos

(18) El nuevo compuesto heterocíclico del punto anterior (1), donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (17):

(1) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(2) Ácido 2-(2-heptenoil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(3) Ácido 2-(2,4-hexadienoil)-7-(2-(2-(1-hexen-1-il)-3-metiloxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(4) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(3-metil-1-hexen-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico

(5) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(1-metil-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(12) Ácido 7-(2-(2-(3,3-dimetil-1-buten-1-il)-5-metiloxazol-4-il)etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(13) Ácido 2-(2,4-hexadienoil)-7-(2-(2-(3-metoxi-1-propen-1-il)-5-metiloxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(14) Ácido 7-(2-(2-(2-ciclopropilvinil)-5-metiloxazol-4-il)etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(15) Ácido 7-(2-(2-(2-ciclohexilvinil)-5-metiloxazol-4-il)etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico,

(16) Ácido 2-(3-butenil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico, y

(17) Ácido 7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi)-2-(4-pentenil)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico

o una sal farmacéuticamente aceptable de los mismos

[19] El nuevo compuesto heterocíclico del punto anterior [1], donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (8):

(1) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(2) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(3) Ácido 2-(2-heptenoil)-7-[2-(8-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(4) Ácido 2-(2,4-hexadienoil)-7-[2-(2-(trans-1-hexen-1-il)-5-metioxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(5) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(5-metil-trans-1-hexen-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(3) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(3-metil-trans-1-buten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(4) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(2-trans-1-metilciclohexen-1-il)vinil)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(5) Ácido 7-[2-(2-(3,3-dimetil-trans-1-buten-1-il)-5-metioxazol-4-il)etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico, y

(6) Ácido 2-(2,4-hexadienoil)-7-[2-(2-(3-metoxi-trans-1-propen-1-il)-5-metioxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

o una sal farmacéuticamente aceptable de los mismos

[21] El nuevo compuesto heterocíclico del punto anterior [1], donde el compuesto de la fórmula (I) son los siguientes (1) o (2)

(1) Ácido 7-[2-(2-(trans-2-ciclopentilvinil)-5-metioxazol-4-il)etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(6) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(1-metil-trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(7) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(1-metil-trans-1-buten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico y

(8) Ácido 2-(2-hexenoil)-7-[2-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

o una sal farmacéuticamente aceptable de los mismos

[20] El nuevo compuesto heterocíclico del punto anterior [1], donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (6):

(1) Ácido 7-[2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi]-2-(2,3,3,3-pentafluoropropionil)-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(2) Ácido 7-[2-(2-(4,4-dimetil-trans-1-penten-1-il)-5-metioxazol-4-il)etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(2) Ácido 7-[2-(2-(trans-2-ciclohexilvinil)-5-metioxazol-4-il)etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

o una sal farmacéuticamente aceptable de los mismos

[22] El nuevo compuesto heterocíclico del punto anterior [1] donde el compuesto de la fórmula (I) son los siguientes (1) o (2)

(1) Ácido 2-(3-butenil)-7-[2-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

(2) Ácido 7-[2-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etoxi]-2-(4-pentenil)-1,2,3,4-tetrahidroisquinolin-(3B)-carboxílico,

o una sal farmacéuticamente aceptable de los mismos

[23] El nuevo compuesto heterocíclico del punto anterior [1], donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (9)

(1) Ácido 2-(2,4-hexadienil)-7-[2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico,

(2) Ácido 7-[2-[2-(trans-2-ciclopentilvinil)oxazol-4-il]etoxi]-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico,

(3) Ácido 7-[2-[2-(trans-2-ciclohexilvinil)oxazol-4-il]etoxi]-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico,

(4) Ácido 2-(2-heptenil)-7-[2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico,

(5) Ácido 2-(2-octenil)-7-[2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico,

(6) Ácido 2-(2,4-hexadienil)-7-[2-[2-(trans-1-hepten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico,

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(7) Ácido 2-(2,4-hexadienil)-7-[2-[2-(1-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico

(8) Ácido 2-(2,4-hexadienil)-7-[2-[2-(1-metil-trans-1-buten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico y

(9) Ácido 2-(2,4-hexadienil)-7-[2-[2-(5-metil-trans-1-hepten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(3R)-carbonílico,

o una sal farmacéuticamente aceptable de los mismos

(24) Una composición farmacéutica que contiene el nuevo compuesto heterocíclico de cualquiera de los puntos anteriores [1] a [23], o una sal farmacéuticamente aceptable de los mismos

(25) Un agente farmacéutico que contiene el nuevo compuesto heterocíclico de cualquiera de los puntos anteriores [1] a [23], o una sal farmacéuticamente aceptable de los mismos, cuyo agente está seleccionado del grupo que consiste en un agente hipoglucémico, un agente hipolipídico, un mejorador de la resistencia a la insulina, un agente terapéutico de diabetes, un agente

terapéutico de complicaciones diabéticas, un mejorador de la tolerancia a la g.-cose, un agente antiarterioesclerosis, un agente antiobesidad, un agente antiinflamatorio, un agente para la profilaxis o tratamiento de enfermedades mediadas por PPAR o un agente para la profilaxis o el tratamiento del síndrome X

(26) Un método para la profilaxis o el tratamiento de hiperglucemia, hiperlipidemia, enfermedades causadas por la resistencia a la insulina, diabetes, una complicación diabética, tolerancia alterada a la glucosa, arterioesclerosis, obesidad, inflamación, enfermedad mediada por PPAR o el síndrome X, que comprende la administración a un paciente de una cantidad de eficacia farmacéutica del compuesto heterocíclico de cualquiera de los puntos anteriores [1] a [23] o una sal farmacéuticamente aceptable de los mismos

(27) Uso de un nuevo compuesto heterocíclico de cualquiera de los puntos anteriores [1] a [23] o una sal farmacéuticamente aceptable del mismo para la preparación de una composición farmacéutica para la profilaxis o el tratamiento de hiperglucemia, hiperlipidemia enfermedades causadas por la resistencia a la insulina, diabetes complicación diabética tolerancia alterada a la glucosa,

arterioesclerosis, obesidad, inflamación, enfermedad mediada por PPAR o el síndrome X

Descripción detallada de la invención

Cada símbolo usado en la presente memoria se explica a continuación

El alquilo C₁₋₆ para R', R', R' y R'' es un alquilo de cadena lineal o ramificada que tiene 1 a 6 átomos de carbono, como metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo y similares, preferentemente metilo, etilo, propilo y isopropilo

El alquilo C₁₋₆ para R', R'' y R'' es un alquilo de cadena lineal o ramificada que tiene 1 a 6 átomos de carbono, como metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, hexilo y similares, preferentemente metilo, etilo, propilo, ter-butilo, butilo, isobutilo e isopentilo

El alquilo C₁₋₆ para R', R' y R'' es un alquilo de cadena lineal o ramificada que tiene 1 a 6 átomos de carbono, como metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, hexilo, heptilo, octilo y similares,

preferentemente metilo etilo, propilo, ter-butilo, butilo, pentilo y hexilo

El alquilo C_{3-8} para R^3 es un alquilo de cadena lineal o ramificada que tiene 3 a 8 átomos de carbono como pentilo, isopentilo, neopentilo, hexilo, heptilo, octilo y similares, preferentemente pentilo, neopentilo y hexilo

En el alquilo C_{3-8} opcionalmente sustituido por halógeno para R^3 , el halógeno es átomo de cloro, átomo de bromo, átomo de yodo o átomo de flúor. El alquilo C_{3-8} es un alquilo de cadena lineal o ramificada que tiene 3 a 8 átomos de carbono, como etilo, propilo, isopropilo, butilo, isobutilo, ter-butilo, pentilo, neopentilo, hexilo y similares. El alquilo C_{3-8} sustituido por halógeno está ejemplificado por 2-cloroetilo, 2-bromoetilo, 2-yodoetilo, 2-fluoroetilo, 1,2-difluoroetilo, 2,2,2-trifluoroetilo, pentafluoroetilo, 2,2,3,3-tetrafluoropropilo, 3,3,3-trifluoropropilo, 4,4,4-trifluorobutilo, 5,5,5-trifluoropentilo, 6,6,6-trifluorohexilo y similares, preferentemente 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo, pentafluoroetilo y 2,2,3,3-tetrafluoropropilo.

En el alquilo C_{3-8} opcionalmente sustituido por halógeno para R^3 y R^{10} , el halógeno es átomo de cloro, átomo

ciclohexilo, cicloheptilo, ciclooctilo y similares, preferentemente ciclohexilo y cicloheptilo.

El alqueno C_{3-8} para R^3 y R^{10} es un alqueno de cadena lineal o ramificada que tiene 3 a 8 átomos de carbono, como vinilo, 1-propenilo, 2-propenilo, isopropenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 1-hexenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, 1-heptenilo, 2-heptenilo, 3-heptenilo, 4-heptenilo, 5-heptenilo, 6-heptenilo, 1-octenilo, 2-octenilo, 3-octenilo, 4-octenilo, 5-octenilo, 6-octenilo, 7-octenilo y similares, preferentemente 1-propenilo, 1-butenilo, 1-pentenilo y 1-hexenilo.

El alqueno C_{3-8} para R^3 es un alqueno de cadena lineal o ramificada que tiene 3 a 8 átomos de carbono, como vinilo, 1-propenilo, 2-propenilo, isopropenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 1-hexenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo y similares, preferentemente 3-butenilo, 4-pentenilo y 5-hexenilo.

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de bromo, átomo de yodo o átomo de flúor. El alquilo C_{3-8} es un alquilo de cadena lineal o ramificada que tiene 3 a 8 átomos de carbono, como metilo, etilo, propilo, isopropilo, butilo, isobutilo, ter-butilo, pentilo, neopentilo, hexilo y similares. El alquilo C_{3-8} sustituido por halógeno está ejemplificado por fluoroetilo, difluoroetilo, trifluoroetilo, cloroetilo, dicloroetilo, tricloroetilo, bromoetilo, dibromoetilo, tribromoetilo, 2-cloroetilo, 2-bromoetilo, 2-yodoetilo, 2-fluoroetilo, 1,2-difluoroetilo, 2,2,2-trifluoroetilo, pentafluoroetilo, 2,2,3,3-tetrafluoropropilo, 3-fluoropropilo, 3,3-difluoropropilo, 3,3,3,3-tetrafluoropropilo, 3,3,3-trifluoropropilo, 4,4,4-trifluorobutilo, 5,5,5-trifluoropentilo, 6,6,6-trifluorohexilo y similares, preferentemente 3-fluoropropilo, 3,3-difluoropropilo, trifluoroetilo, 2,2,2-trifluoroetilo, 1,2-difluoroetilo, 3,3,3-trifluoropropilo y 3,3,3,3-tetrafluoropropilo.

El cicloalquilo C_{3-8} para R^3 y R^{10} es cicloalquilo que tiene 3 a 8 átomos de carbono, como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y similares, preferentemente ciclopropilo, ciclobutilo, ciclohexilo y cicloheptilo.

El cicloalquilo C_{3-8} para R^3 es cicloalquilo que tiene 4 a 8 átomos de carbono como ciclohexilo, cicloheptilo

Como anillo para R^3 , R^4 , R^{10} , R^{11} , R^{12} y R^{13} , están ejemplificados fenilo, naftilo y similares, preferentemente el fenilo.

Como heterociclo aromático para R^3 , R^{10} y R^{14} , se prefiere un heterociclo monocíclico y un heterociclo fundido que tiene al menos un heteroátomo seleccionado del grupo que consiste en átomo de oxígeno, átomo de nitrógeno y átomo de azufre. El heterociclo fundido en la presente invención es un sistema bicíclico, que comprende uno que tiene heteroátomos en ambas anillas. El heterociclo monocíclico preferido es un anillo de 5 ó 6 miembros. El heterociclo que constituye un heterociclo fundido preferible es un heterociclo de 5 ó 6 miembros, y el anillo sin un heterociclo que constituye un heterociclo fundido preferible es un anillo de 5 ó 6 miembros. El heterociclo aromático es, por ejemplo, heterociclo monocíclico como furilo, tienilo, piridilo, imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, triazolilo, tiadiazolilo, sisdiazolilo, piridinilo, pirimidinilo o pirazinilo y similares; un heterociclo fundido como indolilo, isoindolilo, indolinilo, isoindolinilo, indazolilo, benzofuranilo, benzo[1,2-b]oxazolilo, benzimidazolilo, benzoxazolilo, benzotriazolilo, quinolilo, isoquinolilo, benzoxazinilo, benzotiazinilo, furo[2,3-b]piridilo, tieno[2,3-b]piridilo, naftiridinilo.

imidazopiridilo, oxazopiridilo, tiazopiridilo y similares, que son preferentemente furilo, tienilo, piridilo, oxazolilo, tiazolilo, indolilo, indolinilo, benzofuranilo, benzotiofuranilo, quinolilo y isoquinolilo

El cicloalquilo C_{3-6} -alquilo C_{1-3} para R^2 y R^3 es aquel donde la parte cicloalquilo tiene 3 a 6 átomos de carbono y la parte alquilo es un alquilo de cadena lineal o ramificada que tiene 1 a 3 átomos de carbono, como ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, cicloheptilmetilo, ciclooctilmetilo, ciclopropiletilo, ciclobutiletilo, ciclopentiletilo, ciclohexiletilo, cicloheptiletilo, ciclooctiletilo, ciclopropilpropilo, cicloheptilpropilo, ciclooctilpropilo, ciclohexilpropilo, cicloheptilpropilo, ciclooctilpropilo, 1-metilciclohexil-1-ilo, 1-metilciclohexil-1-ilo y similares. Los preferidos son ciclopropilmetilo, ciclopropiletilo, 1-metilciclohexil-1-ilo, 1-metilciclohexil-1-ilo, ciclopentilmetilo y ciclohexilmetilo.

El alcanoil C_{1-4} -alquilo C_{1-4} para R^2 es aquel donde la parte alcanoil es un alquilo de cadena lineal o ramificada que tiene 1 a 4 átomos de carbono y la parte alquilo es un alquilo de cadena lineal o ramificada que tiene 1 a 4 átomos de carbono, como metanimetilo, etanimetilo,

átomo de halógeno (por ejemplo, cloro, bromo, yodo, flúor), nitró, amina y similares. El número del sustituyente es preferentemente 1 ó 2.

El alquiltio C_{1-4} -alquilo C_{1-4} para R^2 y R^3 es aquel donde la parte alquiltio de la parte alquiltio es un alquiltio de cadena lineal o ramificada que tiene 1 a 4 átomos de carbono y la parte alquilo es un alquilo de cadena lineal o ramificada que tiene 1 a 4 átomos de carbono, como metiltioetilo, metiltioetilo, metiltiopropilo, metiltiobutilo, metiltiopentilo, metiltiohexilo, etiltioetilo, etiltioetilo, etiltiopropilo, etiltiobutilo, etiltiopentilo, etiltiohexilo, propiltioetilo, propiltiopropilo, propiltiobutilo, propiltiopentilo, propiltiohexilo, isopropiltioetilo, butiltioetilo, butiltioetilo, butiltiopropilo, butiltiobutilo, butiltiopentilo, butiltiohexilo y similares. Se prefieren metiltioetilo, metiltioetilo, etiltioetilo, etiltioetilo, isopropiltioetilo y metiltiopropilo.

El alquilo C_{1-4} sustituido por $(R^2)_m$, donde R^2 es opcionalmente el mismo que el otro R^2 y es un átomo de hidrógeno o alquilo C_{1-4} , para R^3 es aquel donde la parte alquilo, que es alquilo que tiene 1 a 4 átomos de carbono, es sustituido por $(R^2)_m$ antes mencionado. Los ejemplos de

propiloximetilo, isopropiloximetilo, butoximetilo, metoxietilo, etoxietilo, propiloxietilo, butoxietilo, metoxipropilo, etoxipropilo, propiloxipropilo, butoxipropilo, metoxibutilo, etoxibutilo, propiloxibutilo, butoxibutilo, metoxipentilo, etoxipentilo, propiloxipentilo, butoxipentilo, metoxihexilo, etoxihexilo, propiloxihexilo, butoxihexilo y similares. Se prefieren metoximetilo, metoxietilo, etoximetilo, propiloximetilo, isopropiloximetilo y etoxietilo.

El arilalquilo C_{1-4} opcionalmente sustituido para R^2 es arilo sustituido por al menos un alquilo de cadena lineal o ramificada que tiene 1 a 3 átomos de carbono, como aquel donde la parte arilo es fenilo, naftilo y similares y la parte alquilo es un alquilo de cadena lineal o ramificada que tiene 1 a 3 átomos de carbono. Cuando no está sustituido por el sustituyente antes mencionado, es, por ejemplo, bencilo, 1-naftilmetilo, 2-naftilmetilo, 2-feniletilo, 2-(1-naftil)etilo, 2-(2-naftil)etilo, 2-fenilpropilo, 3-(1-naftil)propilo, 3-(2-naftil)propilo, 1-feniletilo, 2-fenilpropilo, 1-(1-naftil)etilo, 1-(2-naftil)etilo, 1-(1-naftil)propilo, 1-(2-naftil)propilo, 2-(1-naftil)propilo, 2-(2-naftil)propilo y similares. Se prefieren bencilo, 2-feniletilo, 3-fenilpropilo, 1-naftilmetilo y 2-naftilmetilo. Los ejemplos del sustituyente incluyen alquilo C_{1-4} , alcanoil C_{1-4} , hidrógeno,

este alquilo C_{1-4} sustituido por $(R^2)_m$ incluyen aminometilo, etilaminometilo, dimetilaminometilo, aminometilo, metilaminometilo, dimetilaminometilo, aminopropilo, dimetilaminopropilo, aminobutilo, aminopentilo, aminohexilo, dietilaminometilo, dietilaminopentilo, etilaminopentilo y similares. Se prefieren aminometilo, etilaminometilo, dimetilaminometilo, aminometilo, metilaminometilo, dimetilaminometilo, aminopropilo y dimetilaminopropilo.

R^1 es preferentemente un átomo de hidrógeno.

Preferentemente, R^1 es $-CO-C(R^1)-C(R^1)-R^1$, donde R^1 es un átomo de hidrógeno y R^2 es alquilo C_{1-4} o alquenilo C_{1-4} , o $-CO-C(R^1)-R^1$ donde R^1 es alquilo C_{1-4} o alquenilo C_{1-4} .

En la fórmula (II), $Y-(CH_2)_n-O-$ está enlazado preferentemente a la posición 7 del esqueleto de una tetrahidroisquinolina. En $Y-(CH_2)_n-O-$, n es preferentemente 1.

Y es preferentemente un grupo de la fórmula



donde cada símbolo es tal como se definió con anterioridad

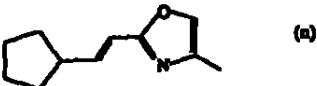
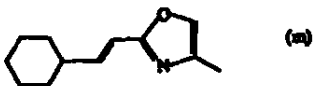
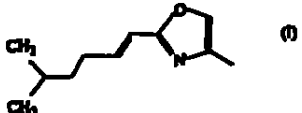
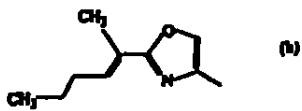
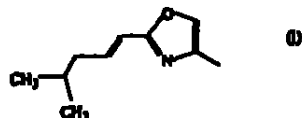
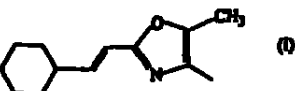
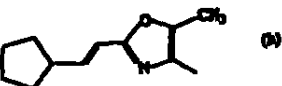
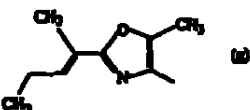
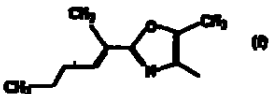
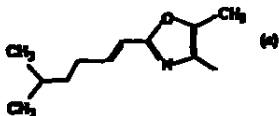
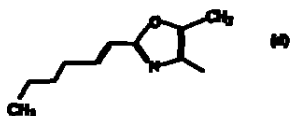
Más preferentemente, Y es aquel donde, en la fórmula antes mencionada,

(1) R' es un átomo de hidrógeno o alquilo C₁₋₄, R'' es R¹³-C(R¹⁴)-C(R¹⁵)-, donde R' es opcionalmente el mismo que el otro R' y es un átomo de hidrógeno o alquilo C₁₋₄ y R¹³ es alquilo C₁₋₄, alquenilo C₂₋₃ o arilo,

(2) R' es un átomo de hidrógeno o alquilo C₁₋₄, R'' es R¹³-S-, donde R¹³ es alquilo C₁₋₄ o arilo y S es un átomo de azufre,

(3) R' es un átomo de hidrógeno o alquilo C₁₋₄ y R'' es alquilo C₂₋₃ o cicloalquilo C₃₋₄,

(4) R' es un átomo de hidrógeno o alquilo C₁₋₄, R'' es R¹³-C(R¹⁴)-C(R¹⁵)-, donde R' es un átomo de hidrógeno y R¹³ es cicloalquilo C₃₋₄, y más preferentemente Y es aquel donde, en la fórmula antes mencionada,

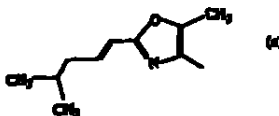
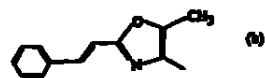
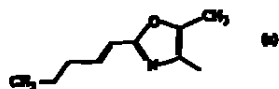


(5) R' es alquilo C₁₋₄, R'' es R¹³-C(R¹⁴)-C(R¹⁵)-, donde R' es opcionalmente el mismo que el otro R' y es un átomo de hidrógeno o alquilo C₁₋₄, R¹³ es alquilo C₁₋₄ y R es un átomo de oxígeno, o

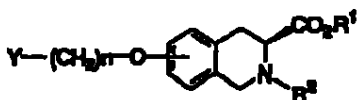
(6) R' es alquilo C₁₋₄, R'' es R¹³-C(R¹⁴)-C(R¹⁵)-, donde R' es un átomo de hidrógeno, R¹³ es arilo, y R es un átomo de oxígeno

X para Y es preferentemente un átomo de oxígeno

De particular preferencia, Y está seleccionada de los siguientes (a) a (n)



El compuesto heterocíclico (II) comprende estereoisómeros debido a un carbono asimétrico en la posición 3 del carbono del anillo de la 1,2,3,4-tetrahidroisquinolina. La configuración más preferible es



donde R^1 , R^2 , Y y n son tal como se definieron con anterioridad

Cuando, en la fórmula (I), R^1 es $-CO-C(R^3)-C(R^4)-R^5$ donde R^3 y R^4 son tal como se definieron con anterioridad, R^5 es $R^6-C(R^7)-C(R^8)-$, donde R^6 y R^8 son tal como se definieron con anterioridad, o Y es $R^9-C(R^{10})-N-O-$, donde R^9 y R^{10} son tal como se definieron con anterioridad, están presentes los estereoisómeros (forma E y forma Z) en el doble enlace o la parte oxima, cuyos dos isómeros están comprendidos en la presente invención

El compuesto (I) de la presente invención puede formar una sal farmacológicamente aceptable. Cuando el compuesto (I) tiene un grupo básico, puede formarse una sal de adición ácida. El ácido para formar esta sal de adición ácida no está limitado en particular, ya que puede formar una sal con una parte básica y es un ácido farmacológicamente aceptable. Los ejemplos del ácido incluyen ácidos inorgánicos como ácido clorhídrico, ácido sulfúrico, ácido fosfórico, ácido nítrico y similares, y

(3) Ácido 2-(2-benzimidazol)-7-[2-(5-metil-2-estirilmanol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(4) Ácido 7-[2-(5-metil-2-estirilmanol-4-il)etoxi]-2-pentilmanol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(5) Ácido 2-(2-heptanol)-7-[2-(5-metil-2-estirilmanol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(6) Ácido 2-(2,4-benzodienol)-7-[2-(5-metil-2-(1-pentan-1-il)manol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(7) Ácido 2-(2-heptanol)-7-[2-(5-metil-2-(1-pentan-1-il)manol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(8) Ácido 2-(2-benzimidazol)-7-[2-(5-metil-2-(1-pentan-1-il)manol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

Ácidos orgánicos como ácido oxálico, ácido fumárico, ácido málico, ácido cítrico, ácido tartárico, ácido metanesulfónico, ácido taluensulfónico y similares

Cuando el compuesto (I) tiene un grupo ácido como un grupo carbonilo y similares, pueden formarse por ejemplo sales de metales alcalinos (por ejemplo, sal de sodio, sal de potasio y similares), sales de metales alcalinotérreos (por ejemplo, sal de calcio, sal de magnesio y similares), sales de bases orgánicas (por ejemplo, sal de tert-butilamina, sal de trietilamina, sal de dicitclohexilamina, sal de etanolamina, sal de piridina, y similares) y otros

Los ejemplos del compuesto heterocíclico de la fórmula (I) y una sal farmacológicamente aceptable de los mismos incluyen los siguientes:

(1) Ácido 2-(2,4-benzodienol)-7-[2-(5-metil-2-estirilmanol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(2) Ácido 2-(2-heptanol)-7-[2-(5-metil-2-estirilmanol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

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(9) Ácido 2-(2,4-benzodienol)-7-[2-(5-metil-2-(1-pentan-1-il)manol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(10) Ácido 2-(2,4-benzodienol)-7-[2-(5-metil-2-(1-pentilmanol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(11) Ácido 7-[2-(2-ciclopentil-5-metilmanol-4-il)etoxi]-2-(2,4-benzodienol)-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico

(12) Ácido 7-[2-(2-ciclohexil-5-metilmanol-4-il)etoxi]-2-(2,4-benzodienol)-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(13) Ácido 7-[2-(2-benzilaminotilmanol-5-il)etoxi]-2-(2-heptanol)-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(14) Ácido 7-[2-(2-butirilaminotilmanol-5-il)etoxi]-2-(2-heptanol)-1,2,3,4-tetrahidroisoquinolina-(3B)-carboxílico,

(18) Ácido 2-(2-heptenoil)-7-(2-(4-metil-2-(feniletildienamino)-5-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico, y

(19) Ácido 2-(2-heptenoil)-7-(2-(1-feniletildienamino)-5-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

y sales farmacéuticamente aceptables de los mismos

De los ejemplos antes mencionados (1)-(19), se prefieren particularmente los siguientes compuestos (1)-(3) y sales farmacéuticamente aceptables de los mismos, porque tienen mayor acción hipotensiva, acción hipolipidémica en sangre, acción mejoradora de la resistencia a la insulina y acción que activa al PPAR (receptor activado por el proliferador de peroxisomas):

(1) Ácido 7-(2-(5-metil-2-etirilexanol-4-il)etoni)-2-pentafluoropropionil-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(2) Ácido 2-(2-heptenoil)-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico, y

(3) Ácido 2-(2-hexenoil)-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico

Los siguientes compuestos (1)-(17), y sales farmacéuticamente aceptables de los mismos son ejemplos preferidos de la presente invención

(1) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(2) Ácido 2-(2-heptenoil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico

(3) Ácido 2-(2,4-hexadienoil)-7-(2-(2-(1-hexen-1-il)-5-metiloxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(4) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(5-metil-1-hexen-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

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(5) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(1-metil-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(6) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(1-metil-1-buten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(7) Ácido 2-(2-heptenoil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(8) Ácido 7-(2-(5-metil-2-(1-penten-1-il)oxazol-4-il)etoni)-2-(2,2,3,3,3-pentafluoropropionil)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(9) Ácido 7-(2-(2-(4,4-dimetil-1-penten-1-il)-5-metiloxazol-4-il)etoni)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(10) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(3-metil-1-buten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico

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(11) Ácido 2-(2,4-hexadienoil)-7-(2-(5-metil-2-(2-(1-metilciclohexan-1-il)vinil)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(12) Ácido 7-(2-(2-(3,3-dimetil-1-buten-1-il)-5-metiloxazol-4-il)etoni)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico

(13) Ácido 2-(2,4-hexadienoil)-7-(2-(2-(3-metil-1-propen-1-il)-5-metiloxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico

(14) Ácido 7-(2-(2-(2-ciclopentilvinil)-5-metiloxazol-4-il)etoni)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(15) Ácido 7-(2-(2-(2-ciclohexilvinil)-5-metiloxazol-4-il)etoni)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico,

(16) Ácido 2-(3-butenil)-7-(2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolina-(3B)-carbonílico, y

(17) Ácido 7-(2-[5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il]etoxi)-2-(4-pentenil)-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico

Además los siguientes compuestos (1)-(8), y sales farmacéuticamente aceptables de los mismos son ejemplos preferidos de la presente invención

(1) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

(2) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

(3) Ácido 2-(2-heptenoil)-7-[2-[5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

(4) Ácido 2-(2,4-hexadienoil)-7-[2-[2-(trans-1-hexen-1-il)-3-metiloxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

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(5) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(3-metil-trans-1-hexen-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico

(6) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(1-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

(7) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(1-metil-trans-1-buten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico, y

(8) Ácido 2-(2-hexenoil)-7-[2-[5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico

Además, los siguientes compuestos (1)-(6), y sales farmacéuticamente aceptables de los mismos son ejemplos preferidos de la presente invención:

(1) Ácido 7-[2-[5-metil-2-(trans-1-penten-1-il)oxazol-4-il]etoxi]-2-(2,2,3,3-pentafluoropropionil)-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico

(2) Ácido 7-[2-[2-(4,4-dimetil-trans-1-penten-1-il)-3-metiloxazol-4-il]etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

(3) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(3-metil-trans-1-buten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

(4) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(2-trans-(1-metilciclohexen-1-il)vinil)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico,

(5) Ácido 7-[2-[2-(3,3-dimetil-trans-1-buten-1-il)-3-metiloxazol-4-il]etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico, y

(6) Ácido 2-(2,4-hexadienoil)-7-[2-[2-(3-metoxi-trans-1-propen-1-il)-5-metiloxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico

Por otra parte, los siguientes compuestos (1) y (2), y sales farmacéuticamente aceptables de los mismos son ejemplos preferidos de la presente invención:

(1) Ácido 7-[2-[2-(trans-2-ciclohexilvinil)-3-metiloxazol-4-il]etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico y

(2) Ácido 7-[2-[2-(trans-2-ciclohexilvinil)-3-metiloxazol-4-il]etoxi]-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico

Adicionalmente, los siguientes compuestos (1) y (2), y sales farmacéuticamente aceptables de los mismos son ejemplos preferidos de la presente invención

(1) Ácido 2-(3-butenil)-7-[2-[5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico, y

(2) Ácido 7-[2-[5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-2-(4-pentenil)-1,2,3,4-tetrahidroisquinolina-(38)-carbonílico

Por otra parte, los siguientes compuestos (1)-(9), y sales farmacéuticamente aceptables de los mismos son ejemplos preferidos de la presente invención:

(1) ácido 2-(2,4-hexadienoil)-7-[2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico,

(2) ácido 7-[2-[2-(trans-2-ciclopentilvinil)oxazol-4-il]etoxi]-2-[2,4-hexadienoil]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico,

(3) ácido 7-[2-[2-(trans-2-ciclopentilvinil)oxazol-4-il]etoxi]-2-[2,4-hexadienoil]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico,

(4) ácido 2-(2-heptenoil)-7-[2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico,

(5) ácido 2-(2-hexenoil)-7-[2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico,

(6) ácido 2-(2,4-hexadienoil)-7-[2-[2-(trans-1-hexen-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico,

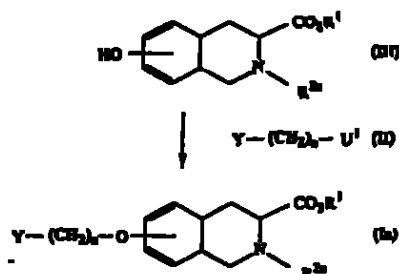
(7) ácido 2-(2,4-hexadienoil)-7-[2-[2-(1-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico,

(8) ácido 2-(2,4-hexadienoil)-7-[2-[2-(1-metil-trans-1-buten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico, y

(9) ácido 2-(2,4-hexadienoil)-7-[2-[2-(2-metil-trans-1-hexen-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolina-(38)-carbonílico

El compuesto (I) de la presente invención y una sal farmacológicamente aceptable de los mismos puede prepararse por cualquiera de los siguientes métodos de producción

Método de producción 1



donde R¹ y R² son tal como se definieron con anterioridad, R³ es -CO-R⁴, donde R⁴ es tal como se definió con anterioridad, -CO-C(R⁵)-C(R⁶)-R⁷ donde R⁵ y R⁶ son tal como se definieron con anterioridad, -CO-C(R⁵)-R⁷, donde R⁷ es tal como se definió con anterioridad, arilo arilalquilo C₁₋₄ opcionalmente sustituido, alquilo C₁₋₄ opcionalmente sustituido por halógeno, alquenilo C₂₋₄, cicloalquilo C₃₋₄ o cicloalquil C₃₋₄-alquilo C₁₋₄, y U' es hidróxilo y/o un grupo de salida como átomo de halógeno (átomo de flúor, átomo de cloro, átomo de bromo, átomo de yodo) o alcansulfoniloxi (por ejemplo, metansulfoniloxi, etansulfoniloxi, propansulfoniloxi, trifluorometansulfoniloxi y similares), arilsulfoniloxi (por ejemplo, fenilsulfoniloxi y toilsulfoniloxi y similares)

En el método de producción 1, un compuesto que tiene la fórmula (II) (compuesto (II)) se hace reaccionar con un compuesto que tiene la fórmula (III) (compuesto (III)) para producir un compuesto que tiene la fórmula (Ia) (compuesto (Ia))

Método de producción 1-a)

Cuando U' es un grupo hidróxilo, el método de producción 1 incluye una reacción de deshidratación como la reacción

de Mitsunobu (Reagents for Organic Synthesis de Fischer & Fleiser, Vol. 6, 643) y similares. La reacción procede en general, en presencia de un solvente usando un compuesto am y una fosfina. Los ejemplos de compuesto am incluyen di-C₁₋₄alquilasodicarbonilato (por ejemplo, dimetilasodicarbonilato, dietilasodicarbonilato, alisoopropilasodicarbonilato y similares), asodicarbonamida (por ejemplo, 1,1'-azobis(N,N'-dimetilformamida), 1,1'-asodicarbonil)dipiperidina y similares) y otros. Los ejemplos de la fosfina incluyen triarilfosfina (por ejemplo, trifenilfosfina y similares), tri(C₁₋₄alquil)fosfina (por ejemplo, tri-n-butilfosfina, tri-n-hexilfosfina, tri-n-octilfosfina y similares) y otros.

El solvente a usar en el método de producción 1-a está liberado de cualquier limitación particular, ya que es inerte a la reacción. Los ejemplos de ellos incluyen diclorano, acetonitrilo, tetrahidrofuran, cloroformo, cloruro de metileno, cloruro de etileno, benceno, tolueno, xileno, acetato de etilo, N,N'-dimetilformamida, N,N'-dimetilacetamida, dimetilsulfóxido y similares, una mezcla de éstos, y similares.

La cantidad de compuesto (II) a usar en el método de producción 1-a está libre de cualquier limitación particular, y es, en general, de 1-5 moles, preferentemente

de 1-3 moles, por 1 mol de compuesto (III). La cantidad de compuesto así y la función a usar es en general de 1-3 moles preferentemente de 1-1.5 moles, por 1 mol de compuesto (III).

Mientras las condiciones de reacción en el método de producción 1-a, como la temperatura de reacción, el tiempo de reacción y similares, varían en función del reactivo, el solvente de reacción y similares a usar la reacción se lleva a cabo generalmente de -30°C a 30°C durante 30 minutos a aproximadamente 12 horas.

Método de producción 1-b:

Cuando U^1 es un grupo de salida como átomo de halógeno o alcansulfoniloni (por ejemplo, metansulfoniloni, etansulfoniloni, propansulfoniloni, trifluorometansulfoniloni y similares), arilsulfoniloni (por ejemplo, fenilsulfoniloni toilsulfoniloni y similares) y otros, el método de producción 1-b se lleva a cabo en un solvente similar a aquéllos utilizados en el método de producción 1-a en presencia de una base.

La base a usar en el método de producción 1-b está libre de cualquier limitación particular y está ejemplificada por bases inorgánicas como carbonatos de

similares, y tris[2-(2-metoxietoxi)etil]amina. Se usa preferentemente fluoruro de tetraetilamonio o tris[2-(2-metoxietoxi)etil]amina. La cantidad de catalizador a usar es, en general, de 0.1-1 moles preferentemente de 0.1-0.5 moles, por 1 mol de compuesto (III).

Mientras las condiciones de reacción en el método de producción 1-b, como la temperatura de reacción, el tiempo de reacción y similares, varían en función del reactivo, el solvente de reacción y similares a usar la reacción se lleva a cabo generalmente de -30°C a 130°C durante 30 minutos a aproximadamente 12 horas.

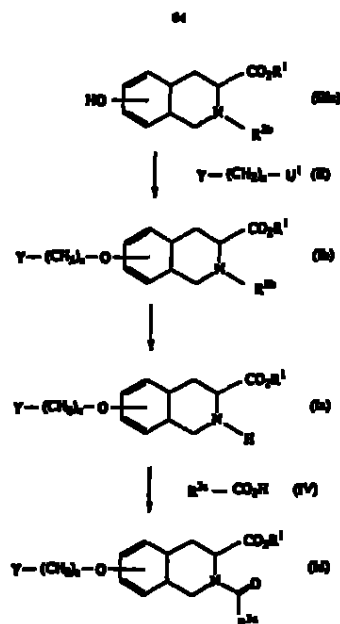
En el método de producción 1-a y el método de producción 1-b, R^1 del compuesto (III) es preferentemente un grupo alquilo C_{1-6} . En este caso, se obtiene un compuesto (Ia), donde R^1 es un grupo alquilo C_{1-6} , el cual se hidroliza por medio de un método conocido por su para obtener un compuesto (Ia), donde R^1 es un átomo de hidrógeno.

Método de producción 2

metales alcalinos (por ejemplo carbonato de sodio, hidrogenocarbonato de sodio, carbonato de potasio, bicarbonato de potasio y similares), hidruídos de metales alcalinos (por ejemplo hidruído de sodio, hidruído de potasio y similares) compuestos de hidruído metálico (por ejemplo hidruído de sodio, hidruído de potasio, hidruído de calcio y similares) y otros; y bases orgánicas como alcoholatos de metales alcalinos (por ejemplo, metóxido de sodio, etóxido de sodio, t-butoxido de potasio y similares), aminas (por ejemplo trietilamina, diisopropilatilamina y similares) y otros.

La cantidad de compuesto (III) a usar en el método de producción 1-b está libre de cualquier limitación particular, y es en general de 1-3 moles preferentemente de 1-3 moles, por 1 mol de compuesto (III). La cantidad de la base a usar es, en general de 1-3 moles, preferentemente de 1-3 moles por 1 mol de compuesto (III).

En el método de producción 1-b, puede usarse un catalizador en un solvente en presencia de una base. El solvente preferido es tolueno y el catalizador está ejemplificado por sales de amonio cuaternarias como bromuro de tetraetilamonio, bromuro de tetraetilamonio, bromuro de tetrabutilamonio, cloruro de tetraetilamonio, fluoruro de tetraetilamonio, bromuro de hexiltrimetilamonio y



donde R^1 , Y , n y U^1 son tal como se definieron con anterioridad, R^2 es un grupo de protección amino, y R^2 es alquilo C_{1-6} opcionalmente sustituido por halógeno, $-\text{C}(\text{R}^3)-\text{C}(\text{R}^4)-\text{R}^5$, donde R^3 y R^4 son tal como se definieron con anterioridad, $-\text{C}(\text{R}^6)-\text{R}^7$ donde R^6 es tal como se define con anterioridad.



donde n es un número entero de 2 a 7

El grupo de protección amino para R^1 está ejemplificado por formilo, monocloroacetilo, dicloroacetilo, tricloroacetilo, trifluoroacetilo, metoxicarbonilo, aminosarbonilo, benciloxicarbonilo, p -nitrobenciloxicarbonilo, difenilmetiloxicarbonilo, metoximetiloxicarbonilo, metoximetiloxicarbonilo, trimetilsililo, 2,2,2-tricloroetoxicarbonilo, 2-metiloximetiloxicarbonilo, $tert$ -butoxicarbonilo (de ahora en más denominado también como Boc), tritilo y similares

En el método de producción 2, el grupo de protección amino de un compuesto que tiene la fórmula (Ib) (compuesto (Ib)) se elimina por medio de un método conocido por se para obtener un compuesto que tiene la fórmula (Ic) (compuesto (Ic)), que se hace reaccionar con un compuesto que tiene la fórmula (IV) (compuesto (IV)) para obtener un compuesto que tiene la fórmula (Id) (compuesto (Id)). El compuesto (Ib) puede producirse haciendo reaccionar el compuesto (II) y un compuesto que tiene la fórmula (IIIa) (compuesto (IIIa)) en el modo de reacción y condiciones de reacción similares a los de la reacción entre compuesto (II) y compuesto (III) en el método de producción 1

se usan estos agentes de condensación, se considera que la reacción precedida por medio de un derivado reactivo de compuesto (IV)

En el método de producción 3, la reacción entre el compuesto (Ic) y el compuesto (IV) se lleva a cabo, en general, en un solvente inerte. Los ejemplos del solvente incluyen acetona, dioxano, acetonitrilo, cloroformo, benceno, cloruro de metileno, cloruro de etileno, tetrahidrofurano, acetato de etilo, N,N -dimetilformamida, piridina, agua y similares, mezclas de éstos y similares. Además, puede usarse una base como trietilamina, piridina, 4-dimetilaminopiridina, carbonato de potasio y similares. Cuando se usa esta base, la cantidad de la base a usar es, en general, de 1-5 moles, preferentemente de 1-3 moles, por 1 mol de compuesto (Ic).

En el método de producción 3, la cantidad de compuesto (IV) a usar es, en general, de 1-5 moles, preferentemente de 1-3 moles, por 1 mol de compuesto (Ic).

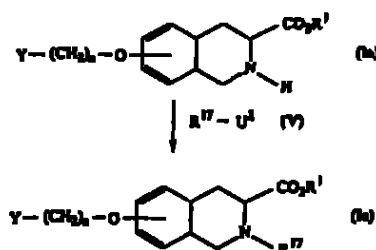
Mientras las condiciones de reacción del compuesto (Ic) y el compuesto (IV) en el método de producción 3, como la temperatura de reacción, el tiempo de reacción y similares, varían en función del reactivo, el solvente de reacción y similares a usar, la reacción se lleva a cabo

En el método de producción 3, el compuesto (IV) se somete a la reacción en sólo una forma de un ácido libre, ésto también en forma de una sal (por ejemplo sal de sodio, potasio, calcio, trietilamina, piridina y similares), un derivado reactivo (por ejemplo haluro ácido como cloruro ácido, bromuro ácido y similares; anhídrido ácido; anhídrido ácido mezclado con ácido fosfórico sustituido (por ejemplo, ácido dialquilfosfórico y similares), con alquilcarbonato (por ejemplo, monometilcarbonato y similares), y otros; amidas activas que son análogas con imidazol y similares; ésteres como éster cianometílico éster de 4-nitrofenilo y similares; y similares

Cuando el compuesto (IV) se usa en forma de un ácido libre o una sal en el método de producción 3, la reacción se lleva a cabo preferentemente, en presencia de un agente de condensación. Los ejemplos del agente de condensación incluyen agentes de deshidratación como compuestos de entredilatación (por ejemplo, N,N -diclorobenzilcarbodiimida, 1-etil-3-(3'-dimetilaminopropil)carbodiimida, N -ciclohexil- N' - ω -terbutiloxetilcarbodiimida, N -ciclohexil- N' -(4-dietilaminociclohexanil)carbodiimida y similares); compuestos de acólido (por ejemplo, N,N' -carbonyldiimidazol, N,N' -tioalidimidazol y similares) y otros; y similares. Cuando

generalmente de -35°C a 150°C durante 30 minutos a aproximadamente 12 horas

Método de producción 3



donde R^1 , Y y n son tal como se definieron con anterioridad, R^{17} es alquilo C_{1-4} opcionalmente sustituido por halógenos, cicloalquilo C_{3-6} , cicloalquil C_{3-6} -alquilo C_{1-4} o arilalquilo C_{6-10} opcionalmente sustituido, y U^1 es un grupo de salida como un átomo de halógeno, grupo alicíclicofenilo (por ejemplo, metanofenilo, etanofenilo, propanofenilo, trifluorometanofenilo y similares), grupo arilalifeno (por ejemplo, fenilofenilo y talisulfofenilo y similares) y otros

En el método de producción 3, el compuesto (Ic) se hace reaccionar con un compuesto que tiene la fórmula (IV)

(compuesto (VI)) para obtener un compuesto que tiene la fórmula (Ic) (compuesto (Ic)).

La reacción entre el compuesto (Ic) y el compuesto (V) para formar el compuesto (Ic) puede llevarse a cabo en un solvente inerte a la reacción en presencia de una base. Los ejemplos del solvente incluyen dioxano, acetonitrilo, tetrahidrofurano, cloroformo, cloruro de metileno, cloruro de etileno, benceno, tolueno, xileno, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, dimetilsulfonido y similares; mezclas de éstos y similares.

La relación de las cantidades molares del compuesto (Ic) y el compuesto (V) a usar está libre de cualquier limitación particular, pero se usan 1-3 moles, preferentemente 1-3 moles, del compuesto (V), por 1 mol de compuesto (Ic).

La base a usar en esta reacción está libre de cualquier limitación particular y se ejemplifica por bases inorgánicas como carbonatos de metales alcalinos (por ejemplo, carbonato de sodio, bicarbonato de sodio, carbonato de potasio, bicarbonato de potasio y similares), hidruros de metales alcalinos (por ejemplo, hidruro de sodio, hidruro de potasio y similares) y otros; alcoholatos de metales alcalinos como metóxido de sodio,

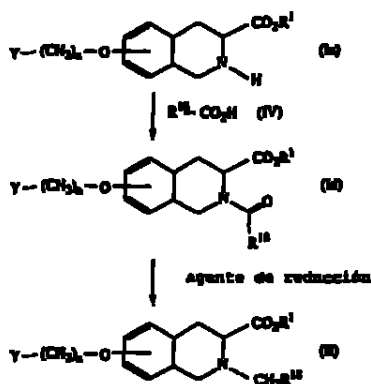
óxido de sodio, t-butoxido de potasio y similares; compuestos de hidruro metálicos como hidruro de sodio, hidruro de potasio, hidruro de calcio y similares; y bases orgánicas como trietilamina, diisopropilietilamina y similares.

La relación de las cantidades molares del compuesto (Ic) y la base a usar está libre de cualquier limitación particular, pero se usan 1-3 moles, preferentemente 1-3 moles de una base, por 1 mol de compuesto (Ic).

Mientras las condiciones de reacción, como la temperatura de reacción, el tiempo de reacción y similares varían en función del reactivo, el solvente de reacción y similares a usar, la reacción se lleva a cabo generalmente de -20° C a 150° C durante 10 minutos a aproximadamente 12 horas.

En este método de producción, R' del compuesto (Ic) es preferentemente un grupo alquilo, obteniéndose el compuesto (Ic) donde R' es un grupo alquilo que se hidraliza por medio de un método conocido por se para obtener el compuesto (Ic), donde R' es un átomo de hidrógeno.

Método de producción 4



donde R', Y y z son tal como se definieron con anterioridad, y R'' es un grupo que forma un grupo de la fórmula: $-CH_2R''$ representa alquilo C₁₋₄ opcionalmente sustituido por halógeno, cicloalquilo C₃₋₆, cicloalquil C₃₋₆-alquilo C₁₋₄ o arilalquilo C₁₋₄ opcionalmente sustituido.

En el método de producción 4, el compuesto (Id) obtenido haciendo reaccionar el compuesto (Ic) con el compuesto (IV) se reduce con un agente de reducción apropiado para producir el compuesto (If). El alquilo C₁₋₄ opcionalmente sustituido por halógeno, cicloalquilo C₃₋₆, cicloalquil C₃₋₆-alquilo C₁₋₄ y arilalquilo C₁₋₄ opcionalmente

sustituido respecto de R'' son tal como se definen respecto de R'.

En el método de producción 4, la reacción entre el compuesto (Ic) y el compuesto (IV) para obtener el compuesto (Id) puede llevarse a cabo en el mismo modo y condiciones de reacción que los del compuesto (Ic) y el compuesto (IV) en el método de producción 2.

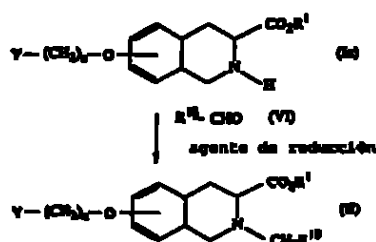
En el método de producción 4, el solvente a usar para la reacción entre el compuesto (Id) y el agente de reducción para obtener compuesto (If) está libre de cualquier limitación particular, ya que no afecta adversamente a la reacción, y está ejemplificado por agua, metanol, etanol, dioxano, acetonitrilo, tetrahidrofurano, cloroformo, cloruro de metileno, cloruro de etileno, benceno, tolueno, xileno, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, dimetilsulfonido y similares; mezclas de éstos y similares.

El agente de reducción a usar para esta reacción no está limitado en particular y puede usarse un complejo de hidruro metálico como hidruro aluminico de litio, cianoborhidruro de sodio, borhidruro de sodio y similares o borano.

La relación de las cantidades molares del compuesto (Id) y el agente de reducción a usar está libre de cualquier limitación particular, pero se usan 1-3 moles, preferentemente 1-2 moles, de agente de reducción por 1 mol de compuesto (Id).

Mientras las condiciones de reacción, como la temperatura de reacción, el tiempo de reacción y similares, varían en función del reactivo, el solvente de reacción y similares a usar, la reacción se lleva a cabo generalmente de -30° C a 50° C durante 30 minutos a aproximadamente 12 horas.

Método de producción 2



donde R¹, Y, n y R¹⁴ son tal como se definiere con anterioridad.

preferentemente 1-3 moles, de compuesto (VI) por 1 mol de compuesto (Id).

La relación de las cantidades molares del compuesto (Id) y el agente de reducción a usar está libre de cualquier limitación particular, pero se usan 1-3 moles, preferentemente 1-2 moles, de agente de reducción por 1 mol de compuesto (Id).

Mientras las condiciones de reacción, como la temperatura de reacción, el tiempo de reacción y similares, varían en función del reactivo, el solvente de reacción y similares a usar, la reacción se lleva a cabo generalmente de -30° C a 50° C durante 30 minutos a aproximadamente 12 horas.

Cuando el compuesto (III) a usar en el método de producción 1 es aquel donde en la fórmula (III), R² es -CO-R¹, donde R¹ es tal como se definió con anterioridad -CO-C(R¹)-C(R¹)-R¹, donde R¹ y R¹ son tal como se definiere con anterioridad, -CO-C≡C-R¹, donde R¹ es tal como se definió con anterioridad alquilo C₁₋₄ opcionalmente sustituido por halógeno, cicloalquilo C₃₋₄, cicloalquil C₃₋₄-alquilo C₁₋₃ o arilalquilo C₁₋₃ opcionalmente sustituido, las reacciones del método de producción 1 pueden llevarse a cabo en el mismo modo de reacción y las mismas condiciones

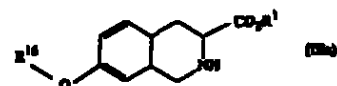
En el método de producción 3, el compuesto (Id) se hace reaccionar con el compuesto (VI) en presencia de un agente de reducción apropiado para producir el compuesto (Ie).

En el método de producción 3, la reacción entre el compuesto (Id) y el compuesto (VI) para obtener el compuesto (Ie) se lleva a cabo por condensación en un solvente que no afecte adversamente la reacción como agua, metanol, etanol, dióxano, acetonitrilo, tetrahidrofurano, cloroformo, cloruro de metileno, cloruro de etileno, benceno, tolueno, nílono, acetato de etilo y N,N-dimetilformamida, N,N-dimetilacetamida, dimetilsulfóxido y similares, mezclas de éstos y similares, en presencia de un agente de reducción apropiado.

El agente de reducción a usar para esta reacción no está limitado en particular y puede usarse un complejo de hidruro metálico como hidruro aluminico de litio, cianhidruro de sodio, borhidruro de sodio y similares o borano.

La relación de las cantidades molares del compuesto (Id) y el compuesto (VI) a usar está libre de cualquier limitación particular, pero se usan 1-3 moles

de reacción que las de la reacción entre el compuesto (Id) y el compuesto (IV) en el método de producción 1 ó la reacción entre el compuesto (Id) y el compuesto (V) en el método de producción 3, o la reacción para obtener el compuesto (II) a partir del compuesto (Id) en el método de producción 4, usando un compuesto de la fórmula (IIIa).



donde R¹ es tal como se definió con anterioridad y R¹⁴ es un átomo de hidrógeno o un grupo de protección hidrómi, (compuesto (IIIa)) como material de partida.

Cuando, en la fórmula (III), R² es un grupo de protección amina, el grupo de protección amina puede introducirse por medio de un método conocido por se, pudiendo producirse un compuesto (III), donde R² es un grupo de protección amina.

Los ejemplos del grupo de protección hidrómi a usar para este método de producción incluyen éteres y acetales como éter metílico, éter isopropílico, éter ter-butílico, éter benzílico, éter alílico, éter metanililico, éter tetrahidropirranílico, éter p-bromobenilico, éter trimetilsililico y similares, y ésteres como formilo,

acetilo, hexacloroacetilo, dicloroacetilo, trifluoroacetilo, metoxicarbonilo, etoxicarbonilo, bromilnicarbonilo, p-nitrobenciloxycarbonilo, 2,2,2-tricloroetoxicarbonilo, hexamilo, octamilsulfonilo, hexamilsulfonilo p-toluenamilsulfonilo y similares

Para la preparación del compuesto (III), R' del compuesto (IIIa) es preferentemente un grupo de protección hidroxilo. El grupo de protección hidroxilo puede eliminarse por medio de un método conocido por se para obtener compuesto (III) fácilmente.

El compuesto heterocíclico (I) obtenido en los métodos de producción 1-3 antes mencionados puede aislarse mediante un método convencional, y purificarse opcionalmente por un método convencional como recristalización, cromatografía preparativa de capa delgada, cromatografía en columna y similares.

El compuesto heterocíclico (I) puede convertirse en una sal farmacológicamente aceptable de los mismos por un método conocido por se.

Una composición farmacéutica que comprende el compuesto heterocíclico (I) o una sal farmacológicamente aceptable del mismo de la presente invención puede contener

El compuesto heterocíclico (I) y una sal farmacológicamente aceptable del mismo de la presente invención muestran una acción hipoglucémica superior, una acción hipolipidémica en sangre, una acción mejoradora de la resistencia a la insulina y una acción que active el PPAR en mamíferos (por ejemplo, humanos, caballos, vacas, perros, gatos, ratas, ratones, hamsters y similares), y son útiles como agente hipoglucémico, agente hipolipidémico, mejorador de la resistencia a la insulina, agente terapéutico de diabetes, agente terapéutico de una complicación diabética, mejorador de la tolerancia a la glucosa, agente antiarterioesclerosis, agente antiobesidad, agente antiinflamatorio, agente para la profilaxis o tratamiento de enfermedad mediada por PPAR o agente para la profilaxis o el tratamiento del síndrome X. Para ser específicos, el compuesto heterocíclico (I) y una sal farmacológicamente aceptable del mismo de la presente invención son útiles para la profilaxis o el tratamiento de diabetes, complicación diabética, hiperlipidemia, arterioesclerosis, hiperglicemia, enfermedades crónicas por la intolerancia a la glucosa resistente a la insulina, enfermedades causadas por la resistencia a la insulina, obesidad, inflamación, enfermedad mediada por PPAR o el síndrome X.

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un aditivo y similares. Como aditivo, figuran como ejemplo un excipiente (por ejemplo, almidón, lactosa, sacarosa, carbonato de calcio, fosfato de calcio y similares), un aglutinante (por ejemplo, almidón goma arábiga, carboximetilcelulosa, hidroxipropilcelulosa, celulosa cristalina y similares), un lubricante (por ejemplo, estearato de magnesio, talco y similares), un desintegrante (por ejemplo, carboximetilcelulosa cálcica, talco y similares), y similares.

Los componentes antes mencionados se mezclan para obtener una preparación para administración oral, como cápsula, comprimido, polvo, gránulo, jarabe en polvo y similares, o una preparación para administración parenteral, como inyección, supositorio y similares, de acuerdo con un método conocido por se.

Mientras que la dosis del compuesto heterocíclico (I) o sal farmacológicamente aceptable del mismo puede variar de acuerdo con el sujeto de administración, el sistema y otras factores, cuando se administra por vía oral a un paciente adulto con, por ejemplo, diabetes, una complicación diabética o hiperlipidemia, la dosis única es de aproximadamente 1 - 500 mg, la cual se administra 1 a 3 veces por día.

La presente invención se detalla por medio de ejemplos y ejemplos de referencia, los cuales no figuran como limitativos.

Ejemplos

Ejemplo 1

2-(2-heptanoil)-7-(2-(5-metil-2-(trans-1-pentan-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolina-(3R)-carbonilato de sodio

(1) Se disolvieron 2-(2-heptanoil)-7-hidroxi-1,2,3,4-tetrahidroisoquinolina-(3R)-carbonilato de metilo (300 mg) y 2-(5-metil-2-(trans-1-pentan-1-il)oxazol-4-il)etilmetansulfonato (630 mg) en tolueno (15 ml), y se agregaron carbonato de potasio (630 mg) e hidrato de cloruro de tetraetilamonio (100 mg). La mezcla se agitó a 60° C durante 10 horas. A la mezcla de reacción se agregó acetato de etilo (50 ml), y la mezcla se lavó con agua (50 ml) y salmuera saturada (50 ml), y se secó (Na₂SO₄). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener 2-(2-heptanoil)-7-(2-(5-metil-2-(trans-1-pentan-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisoquinolina-(3R)-carbonilato de metilo (620 mg).

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¹H-NMR (CDCl₃) δ (ppm): 0.95 (6H, br-t), 1.15-1.75 (6H, m), 2.00-2.45 (4H, m), 2.27 (3H, s), 2.67 (2H, t, J=6 Hz), 3.00-3.30 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J=6 Hz), 4.30-5.70 (3H, m), 6.15 (1H, d, J=15 Hz), 6.35-7.20 (3H, m), 7.64 (1H, d, J=6 Hz)

(2) El compuesto (200 mg) obtenido en el punto (1) antes mencionado se disolvió en una mezcla (5 ml) de tetrahidrofurano-metanol (3:1), y se agregó una solución acuosa de hidróxido de litio 1 M (1.5 ml). La mezcla se agitó a 30° C durante 30 minutos y se acidificó con solución acuosa de ácido cítrico al 10 %. La solución se concentró a presión reducida y el material de goma precipitado se extrajo con acetato de etilo (30 ml). La capa de acetato de etilo se lavó con salmuera saturada (10 ml) y se secó (MgSO₄). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílica para obtener ácido 2-(2-heptanoil)-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico (170 mg). Esto se disolvió en metanol (2 ml) y se agregó una solución de hidróxido de sodio-metanol 0.500 M (0.62 ml), y el metanol se evaporó a presión reducida. El residuo obtenido se disolvió en agua (1 ml) y se liofilizó para obtener el compuesto que figura en el título (170 mg).

sílica para obtener 2-ter-butoxicarbonil-7-[2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoni]-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de metilo (0.97 g).

IR ν (nato) cm⁻¹: 1740, 1690, 1615, 1533, 1505

¹H-NMR (CDCl₃) δ (ppm): 0.89 (3H, t, J=7 Hz), 1.20-1.30 (12H, m), 2.00-2.40 (2H, m), 2.20 (3H, s), 2.69 (2H, t, J=6 Hz), 2.90-3.20 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J=6 Hz), 4.40-4.90 (2H, m), 5.00-5.20 (1H, m), 6.15 (1H, d, J=16 Hz), 6.73 (1H, dt, J=16 l, 6 Hz), 6.90-6.90 (2H, m), 7.01 (1H, d, J=6 Hz)

(2) El compuesto (0.55 g) obtenido en el punto (1) anterior se disolvió en ácido fórmico (3 ml), y se agregó una solución de cloruro de hidrógeno-propanol 0.70 M (0.30 ml) bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 30 minutos y se agregó acetato de etilo (20 ml) a la mezcla de reacción. Tras neutralizar con hidrogenocarbonato de sodio saturado acuoso, se separaron las dos capas y la capa de acetato de etilo obtenida se lavó con salmuera saturada (10 ml) y se secó (MgSO₄). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílica para obtener 7-(2-(5-metil-2-

IR ν (NMR) cm⁻¹: 1653, 1595, 1505

¹H-NMR (DMSO-d₆) δ (ppm): 0.89 (6H, br-t), 1.10-1.75 (6H, m), 1.90-2.30 (4H, m), 2.25 (3H, s), 2.70 (2H, br-t), 3.00-3.30 (2H, m), 4.07 (3H, br-t), 4.20-5.15 (3H, m), 6.19 (1H, d, J=16 Hz), 6.30-6.90 (3H, m), 6.99 (1H, d, J=6 Hz)

Ejemplo 2

Ácido 2-(2,4-bisoxadienil)-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonílico

(1) Se disolvieron 2-ter-butoxicarbonil-7-hidroxi-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de metilo (0.5 g) y 2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etilammoniosulfato (0.67 g) en tolueno (5 ml) y se agregaron carbonato de potasio (0.66 g) e hidrato de fluoruro de tetraetilamonio (0.12 g). La mezcla se agitó a 30° C durante 16 horas. A la mezcla de reacción se agregó acetato de etilo (20 ml), y la mezcla se lavó con agua (20 ml) y salmuera saturada (20 ml), y se secó (MgSO₄). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de

(trans-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de metilo (0.39 g)

IR ν (nato) cm⁻¹: 1742, 1505

¹H-NMR (CDCl₃) δ (ppm): 0.94 (3H, t, J=7 Hz), 1.20-1.70 (2H, m), 2.00-2.40 (2H, m), 2.27 (3H, s), 2.90-3.20 (2H, m), 2.95 (2H, t, J=6 Hz), 3.00-3.30 (1H, m), 3.74 (3H, s), 4.05 (2H, s), 4.14 (2H, t, J=6 Hz), 6.17 (1H, d, J=16 Hz), 6.40-6.90 (1H, m), 6.94 (1H, d, J=2 Hz), 6.99 (1H, dd, J=6 J, 2 Hz), 6.99 (1H, d, J=6 Hz)

(3) El compuesto (0.36 g) obtenido en el punto anterior (2) se disolvió en cloruro de metileno (5 ml), y se agregaron cloruro sódico (0.13 g) y trietilamina (0.17 ml). La mezcla se agitó a temperatura ambiente durante 30 minutos y se agregó acetato de etilo (30 ml). La mezcla se lavó con solución acuosa de ácido cítrico al 10 % (15 ml) y salmuera saturada (15 ml), y se secó (MgSO₄). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílica para obtener 2-(2,4-bisoxadienil)-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoni)-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de metilo (0.4 g)

IR ν (nato) cm⁻¹: 1740, 1655, 1620, 1603, 1506

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.95 (3H, t, J=6.8 Hz), 1.20-1.70 (2H, m), 1.83 (3H, d, J=5.8 Hz), 2.00-2.40 (2H, m), 2.04 (3H, s), 2.87 (2H, t, J=6.7 Hz), 3.00-3.25 (2H, m), 3.89 (2H, s), 4.18 (2H, t, J=6.7 Hz), 4.80-5.65 (3H, m), 6.00-6.90 (7H, m), 7.03 (1H, d, J=8.2 Hz), 7.15-7.55 (1H, m)

(4) El compuesto (0.37 g) obtenido en el punto anterior (3) se disolvió en una mezcla (9.4 ml) de tetrahidrofuran-metanol (3:1), y se agregó una solución acuosa de hidruído de litio 1 N (2.35 ml) y la mezcla se agitó a 50° C durante 30 minutos. La mezcla se acidificó con solución acuosa de ácido cítrico al 10 %, y la mezcla resultante se concentró a presión reducida. El material de goma precipitado se extrae con acetato de etilo (50 ml), y la capa de acetato de etilo se lavó con salmuera saturada (30 ml), y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener el compuesto que figura en el título (0.28 g)

IR v (Kujol) cm^{-1} : 1720, 1651, 1616, 1531, 1504

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.92 (3H, t, J=6.8 Hz), 1.20-1.75 (2H, m), 1.84 (3H, d, J=4.8 Hz), 2.14 (2H, m), 2.22

Los datos de $^1\text{H-NMR}$ eran iguales a los del compuesto del ejemplo 1(1)

Los compuestos de los ejemplos 4-15 se sintetizaron de la misma manera que en los ejemplos 1-3

Ejemplo 4

Ácido 2-(2-heptenil)-7-(2-(5-etil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

IR v (Kujol) cm^{-1} : 2237, 1717, 1664, 1616, 1576, 1506

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.83-1.20 (4H, m), 1.25-1.90 (4H, m), 2.00-2.50 (4H, m), 2.24 (3H, m), 2.80-3.50 (4H, m), 3.80-4.10 (2H, m), 4.35-5.20 (2H, m), 5.30-5.65 (1H, m), 6.18 (1H, d, J=16.0 Hz), 6.45-6.85 (3H, m), 7.01 (1H, d, J=7.8 Hz), 8.80-9.40 (1H, br)

Ejemplo 5

Ácido 2-(2,4-hexadienil)-7-(2-(5-etil-2-oxiriloxazol-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

IR v (Kujol) cm^{-1} : 1729, 1652, 1615, 1575

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(3H, s), 2.63 (2H, br-t), 2.80-3.50 (2H, m), 3.95 (2H, br-t), 4.60-5.10 (3H, m), 5.40-5.65 (1H, m), 6.00-6.80 (3H, m), 7.02 (1H, d, J=8.4 Hz), 7.15-7.55 (1H, m), 8.80-10.50 (1H, br)

Ejemplo 3

2-(2-heptenil)-7-(2-(5-etil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo

El compuesto (210 mg) obtenido en el ejemplo 2(2) se disolvió en cloruro de metileno (2.1 ml), y se agregaron ácido 2-heptenoico (105 mg) y clorhidrato de 1-etil-3-(3'-dimetilaminopropil)carbodiimida (160 mg). La mezcla se agitó a temperatura ambiente durante 1 hora. Se agregó acetato de etilo (20 ml), y la mezcla se lavó con solución acuosa de ácido cítrico al 10 % (15 ml) y salmuera saturada (15 ml) y se secó (Na_2SO_4). El solvente se evaporó a presión reducida, y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener 2-(2-heptenil)-7-(2-(5-etil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (200 mg)

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.03 (3H, br-d), 2.28 (3H, s), 2.82 (2H, br-t), 2.90-3.50 (2H, m), 4.03 (2H, br-t), 4.60-5.10 (3H, m), 5.40-5.65 (1H, m), 6.00-6.80 (3H, m), 6.84 (1H, d, J=16.5 Hz), 7.04 (1H, d, J=8.4 Hz), 7.15-7.55 (2H, m), 8.40-10.20 (1H, br)

Ejemplo 6

Ácido 2-(2-heptenil)-7-(2-(5-etil-2-oxiriloxazol-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

IR v (Kujol) cm^{-1} : 1740, 1653, 1612, 1553, 1506

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.70-1.00 (2H, br), 1.10-1.75 (4H, m), 1.90-2.40 (2H, br), 2.29 (3H, s), 2.80-3.40 (4H, m), 3.75-4.20 (2H, m), 4.55-5.10 (2H, m), 5.40-5.70 (1H, m), 6.33 (1H, d, J=15.7 Hz), 6.55-7.25 (3H, m), 7.30-7.70 (2H, m), 8.00-9.80 (1H, br)

Ejemplo 7

Ácido 2-(2-hexenil)-7-(2-(5-etil-2-oxiriloxazol-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonílico

IR v (Kujol) cm^{-1} : 2235, 1734, 1630, 1580, 1520, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.96, 1.04 (3H, t, t, J=6.7 Hz), 1.35-1.60 (2H, m), 2.10-2.50 (2H, m), 3.20 (3H, s), 2.70-3.50 (4H, m), 3.80-4.15 (2H, m), 4.95-5.20 (2H, m), 5.30-5.60 (2H, m), 6.45-6.70 (2H, m), 7.05 (1H, d, J=16.5 Hz), 7.25-7.45 (6H, m), 7.80-8.00 (1H, br)

Example 8

Acide 7-(2-(1-méthyl-2-oxotétrahydroquinolin-4-yl)éthyl)-2-pentafurancarboxylique-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1732, 1680, 1647, 1614, 1578, 1531, 1506

$^1\text{H-NMR}(\text{CDCl}_3+\text{DMSO}-d_6)$ δ (ppm): 2.34 (3H, s), 2.91 (2H, t, J=6.0 Hz), 3.10-3.30 (2H, m), 4.10 (2H, t, J=6.0 Hz), 4.40-5.30 (3H, m), 6.80-6.90 (2H, m), 6.84 (1H, d, J=16.5 Hz), 6.90-7.25 (2H, m), 7.30-7.60 (5H, m)

Example 9

Acide 2-(2-heptenyl)-7-(2-(5-méthyl-2-oxotétrahydroquinolin-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1732, 1657, 1614, 1545, 1506, 1464

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.75-1.05 (3H, br), 1.10-1.75 (4H, br), 2.00-2.50 (4H, m), 2.30 (3H, s), 2.70-3.40 (4H, m), 3.80-4.30 (2H, m), 4.80-5.10 (2H, m), 5.30-5.70 (1H, m), 6.10-7.70 (13H, m)

Example 10

Acide 2-(2,4-hexadienyl)-7-(2-(5-méthyl-2-oxotétrahydroquinolin-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1730, 1648, 1616, 1456, 1377, 990

$^1\text{H-NMR}(\text{DMSO}-d_6)$ δ (ppm): 1.03 (3H, br-s), 2.27 (3H, s), 2.8-3.4 (4H, m), 4.12 (2H, br-t), 4.2-5.0 (3H, m), 5.10 (1H, br-t), 5.9-7.4 (11H, m)

Example 11

Acide 2-(2,4-hexadienyl)-7-(2-(5-méthyl-2-oxotétrahydroquinolin-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1728, 1653, 1616, 1574, 1508

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.67 (3H, t, J=5.9 Hz), 1.10-1.40 (4H, m), 1.45-1.80 (2H, m), 1.84 (3H, d, J=6.0 Hz), 2.20 (3H, s), 2.65 (2H, t, J=6.1 Hz), 2.73 (2H, br-t), 3.93 (2H, br-t), 4.40-5.10 (3H, m), 5.45-5.70 (1H, m), 5.10-6.80 (5H, m), 7.93 (1H, d, J=6.0 Hz), 7.10-7.50 (1H, m), 9.10-10.00 (1H, br)

Example 12

Acide 7-(2-(2-cyclohexyl-5-méthylcarboxyl-4-yl)éthyl)-2-(2,4-hexadienyl)-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1733, 1652, 1615, 1568

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.0-2.0 (11H, m), 2.20 (3H, s), 2.77 (2H, t, J=6.0 Hz), 2.8-3.4 (3H, m), 3.93 (2H, t, J=6.0 Hz), 4.6-5.0 (2H, m), 5.34 (1H, br-t), 6.0-6.8 (5H, m), 7.62 (1H, d, J=6.0 Hz), 7.1-7.8 (1H, m), 8.0-9.0 (1H, br)

Example 13

Acide 7-(2-(2-cyclohexyl-5-méthylcarboxyl-4-yl)éthyl)-2-(2,4-hexadienyl)-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1733, 1652, 1616, 1456, 1377, 1160, 999

$^1\text{H-NMR}(\text{DMSO}-d_6)$ δ (ppm): 1.0-2.0 (13H, m), 2.20 (3H, s), 2.77 (2H, t, J=6.0 Hz), 2.8-3.4 (3H, m), 4.09 (2H, t, J=6.0 Hz), 4.2-5.0 (2H, m), 5.17 (1H, br-t), 5.8-7.3 (7H, m)

Example 14

Acide 2-(2-heptenyl)-7-(2-(5-méthyl-2-oxotétrahydroquinolin-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1732, 1716, 1651, 1574, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.75-1.05 (3H, m), 1.10-1.70 (4H, m), 2.00-2.40 (2H, m), 2.31 (3H, s), 2.60-3.30 (2H, m), 4.10-4.30 (2H, m), 4.40-5.10 (4H, m), 5.30-5.60 (1H, m), 6.15-7.15 (6H, m), 7.25-7.50 (3H, m), 7.60-7.80 (2H, m)

Example 15

Acide 2-(2-heptenyl)-7-(2-(4-méthyl-2-oxotétrahydroquinolin-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-(3H)-carbonilique

IR v (Nujol) cm^{-1} : 1726, 1612, 1582, 1502

$^1\text{H-NMR}(\text{DMSO}-d_6)$ δ (ppm): 0.70-1.10 (3H, m), 1.20-1.70 (4H, m), 2.00-2.30 (2H, m), 2.29 (3H, s), 2.90-3.60 (3H, m), 4.04 (2H, t, J=5.9Hz), 4.35-4.93 (2H, m), 5.90-6.30 (1H, m), 6.35-6.90 (4H, m), 7.09 (1H, d, J=7.9Hz), 7.35-7.70 (3H, m)

Ejemplo 16

Ácido 7-(2-(2-benzilaminotiazol-5-il)etoni-2-ter-butoxicarbonil-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato

(1) Se disolvieron 2-(2-aminotiazol-5-il)etimetansulfonato (2.43 g) y 2-ter-butoxicarbonil-7-hidroxi-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (2.17 g) en N,N-dimetilformamida (30 ml), y se agregó carbonato de sodio (5.20 g). La mezcla se agitó a 55° C durante 15 horas. A la mezcla de reacción se agregó agua (200 ml), y la mezcla se extrajo tres veces con acetato de etilo (100 ml). La capa de acetato de etilo se lavó dos veces con agua (100 ml) y luego con salmuera saturada (100 ml), y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 7-(2-benzilaminotiazol-5-il)etoni-2-ter-butoxicarbonil-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (2.20 g)

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4.90 (2H, m), 4.95-5.25 (1H, m), 6.35-6.90 (3H, m), 7.04 (1H, d, J=7.9Hz), 7.30-7.70 (3H, m), 7.90-8.20 (2H, m)

(2) El compuesto (533 mg) obtenido en el punto anterior (2) se disolvió en ácido fórmico (2.0 ml), y se agregó una solución de cloruro de hidrógeno-2-propanol 5.78 N (0.30 ml) bajo enfriamiento con hielo. La mezcla se agitó a la misma temperatura durante 15 minutos. La mezcla de reacción se neutralizó con hidrogenocarbonato de sodio saturado acuoso se extrajo con cloroformo (30 ml) y se secó (Na_2SO_4). El cloroformo se evaporó a presión reducida para obtener 7-(2-benzilaminotiazol-5-il)etoni-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (401 mg)

IR v (Kujol) cm^{-1} : 3161, 1744, 1639, 1603, 1582, 1556, 1535, 1501

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 2.90-3.10 (2H, m), 3.19 (2H, t, J=6.1Hz), 3.60-3.80 (1H, m), 3.77 (3H, s), 4.08-4.30 (4H, m), 6.30 (1H, d, J=2.2Hz), 6.74 (1H, dd, J=2.2, 8.4Hz), 6.95-7.10 (2H, m), 7.30-7.60 (3H, m), 7.85-8.10 (2H, m)

(4) El compuesto (400 mg) obtenido en el punto anterior (3) se disolvió en cloruro de metileno (5.0 ml), y se agregaron ácido 2-heptanoico (0.19 ml) y clorhidrato de 1-etil-3-(3'-dimetilaminopropil)carbodiimida (165 mg) bajo

(7)

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.46, 1.51 (9H, s, s), 2.90-3.30 (4H, m), 3.61 (3H, s), 4.07 (2H, t, J=6.3Hz), 4.30-4.90 (4H, m), 4.95-5.25 (1H, m), 6.35-6.90 (3H, m), 7.03 (1H, d, J=8.4Hz)

(2) El compuesto (200 mg) obtenido en el punto anterior (1) se disolvió en N,N-dimetilformamida (5.0 ml), y se agregaron trietilamina (0.25 ml) y cloruro de benzilo (0.16 ml). La mezcla se agitó a 55° C durante 15 horas. A la mezcla de reacción se agregó agua (20 ml), y la mezcla se extrajo tres veces con acetato de etilo (10 ml). La capa de acetato de etilo se lavó dos veces con agua (20 ml) y luego con salmuera saturada (20 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 7-(2-benzilaminotiazol-5-il)etoni-2-ter-butoxicarbonil-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (533 mg)

IR v (Kujol) cm^{-1} : 1746, 1684, 1603, 1582, 1555, 1535, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.46, 1.51 (9H, s, s), 2.90-3.30 (3H, m), 3.61 (3H, s), 4.11 (2H, t, J=6.1Hz), 4.20-

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enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 1 hora, se lavó con solución acuosa de ácido cítrico al 10 % (10 ml) y luego con salmuera saturada (30 ml), y se secó (Na_2SO_4). Se evaporó el cloruro de metileno a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 7-(2-benzilaminotiazol-5-il)etoni-2-(2-heptanoil)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (493 mg)

IR v (Kujol) cm^{-1} : 3165, 1740, 1661, 1616, 1538, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.80-1.10 (3H, m), 1.20-1.70 (4H, m), 2.00-2.50 (2H, m), 3.00-3.45 (4H, m), 3.60 (3H, s), 4.12 (2H, t, J=3.9Hz), 4.30-5.00 (2H, m), 5.40-5.60 (1H, m), 6.35 (1H, d, J=1.5Hz), 6.65-7.20 (4H, m), 7.35-7.70 (3H, m), 7.80-8.15 (2H, m)

(5) El compuesto (490 mg) obtenido en el punto anterior (4) se disolvió en una mezcla (20 ml) de tetrahidrofurano-metanol (3:1), y se agregó una solución acuosa de hidróxido de litio 1 N (3.0 ml). La mezcla se agitó a 50° C durante 30 minutos y se acidificó con solución acuosa de ácido cítrico al 10 %. El solvente se evaporó a presión reducida. Los cristales precipitados se

recogieron por filtración para obtener el compuesto que figura en el título (342 mg)

IR v (NaCl) cm^{-1} : 1734 1655, 1603 1560, 1541 1506

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.90-1.10 (3H, m), 1.20-1.70 (4H, m), 2.00-2.30 (2H, m), 2.80-3.40 (4H, m), 3.80-4.20 (2H, m), 4.50-5.00 (2H, m), 5.50-5.80 (1H, m), 6.00-7.20 (4H, m), 7.30-7.70 (2H, m), 7.80-8.15 (2H, m), 9.00-11.20 (1H, br)

El compuesto del ejemplo 17 es sintético de la misma manera que en el ejemplo 16

Ejemplo 17

Ácido 7-[2-(2-hidroxi-1-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etilmetansulfonato]-1,2,3,4-tetrahidroisquinolin-3(2H)-carboxílico

IR v (NaCl) cm^{-1} : 3172, 1734 1692 1655, 1612, 1562, 1504

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.94 (3H, t, J=7.0Hz), 1.10-1.90 (6H, m), 2.10-2.60 (2H, m), 2.80-3.50 (4H, m), 3.80-4.30 (2H, m), 4.40-5.10 (2H, m), 5.35-5.80 (1H, m), 6.10-7.30 (6H, m), 9.00-11.20 (2H, br)

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.94 (3H, t, J=6.3Hz), 1.40-1.50 (3H, s, s), 1.50-2.00 (1H, m), 2.11 (2H, t, J=6.8Hz), 2.20 (3H, s), 2.87 (2H, t, J=6.8Hz), 3.00-3.25 (2H, m), 3.61 (3H, s), 4.15 (2H, t, J=6.8Hz), 4.45-5.25 (3H, m), 6.15 (1H, d, J=15.8Hz), 6.45-6.80 (3H, m), 7.01 (1H, d, J=6.8Hz)

(2) El compuesto (1,6 g) obtenido en el punto anterior (1) se disolvió en ácido fórmico (8 ml), y se agregó una solución de cloruro de hidrógeno-2-propanol 0,76 N (1,1 ml) bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 15 minutos. A la mezcla de reacción se agregaron acetato de etilo y agua (30 ml cada uno). Tras neutralizar con bicarbonato de sodio, se separaron las dos capas, y la capa de acetato de etilo obtenida se lavó con salmuera saturada (30 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener el compuesto que figura en el título (1,17 g)

IR v (neto) cm^{-1} : 3344, 2955, 2926, 2876, 1730, 1661, 1641, 1612, 1533, 1504

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.94 (3H, t, J=6.3Hz), 1.50-1.95 (1H, m), 2.11 (2H, t, J=6.8Hz), 2.12 (1H, br-s), 2.20

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Ejemplo 18

7-[2-(2-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etilmetansulfonato]-1,2,3,4-tetrahidroisquinolin-3(2H)-carboxilato de metilo

(1) Se disolvieron 2-ter-butoxicarbonil-7-hidroxi-1,2,3,4-tetrahidroisquinolin-3(2H)-carboxilato de metilo (1,8 g) y 2-[2-(2-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etilmetansulfonato] (1,6 g) en tolueno (30 ml) y se agregaron carbonato de potasio (1,35 g) e hidrato de fluoruro de tetraetilamonio (0,2 g). La mezcla se agitó a 90° C durante 13 horas. A la mezcla de reacción se agregó acetato de etilo (30 ml), y la mezcla se lavó sucesivamente con agua (30 ml) y salmuera saturada (30 ml) y se secó (Na_2SO_4). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener 2-ter-butoxicarbonil-7-[2-(2-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etilmetansulfonato]-1,2,3,4-tetrahidroisquinolin-3(2H)-carboxilato de metilo (1,6 g)

IR v (neto) cm^{-1} : 2957 2926, 2872, 1748, 1701 1614, 1533, 1506

(3H, s), 2.87 (2H, t, J=6.8Hz), 2.90-3.10 (2H, m), 3.55-3.80 (1H, m), 3.77 (2H, s), 4.06 (2H, s), 4.14 (2H, t, J=6.8Hz), 6.16 (1H, d, J=15.8Hz), 6.40-6.80 (3H, m), 7.00 (1H, d, J=6.8Hz)

Ejemplo 19

Ácido 2-(2,4-hexadienonil)-7-[2-(2-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etilmetansulfonato]-1,2,3,4-tetrahidroisquinolin-3(2H)-carboxílico

(1) El compuesto (1,15 g) obtenido en el ejemplo 10 se disolvió en cloruro de metileno (20 ml), y se agregaron cloruro de ácido fórmico (0,48 g) y trietilamina (0.6 ml). La mezcla se agitó a temperatura ambiente durante 15 minutos y se agregó cloruro de metileno (30 ml). La mezcla se lavó con agua y salmuera saturada (30 ml cada uno), y se secó (Na_2SO_4). Se evaporó el cloruro de metileno a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener 2-(2,4-hexadienonil)-7-[2-(2-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etilmetansulfonato]-1,2,3,4-tetrahidroisquinolin-3(2H)-carboxilato de metilo (1,36 g)

IR v (neto) cm^{-1} : 1748 1655, 1626, 1533, 1506

¹H-NMR(CDCl₃) δ (ppm): 0.94 (4H, d, J=6 Hz), 1.90-1.95 (4H, m), 2.11 (2H, t, J=7 Hz), 2.28 (3H, s), 2.87 (2H, t, J=6 Hz), 3.00-3.30 (2H, m), 3.60 (2H, m), 4.18 (2H, t, J=6 Hz), 4.50-5.15 (2H, m), 5.40-5.70 (1H, m), 6.00-6.90 (7H, m), 7.04 (1H, d, J=8 Hz), 7.15-7.55 (1H, m).

(2) El compuesto (1.36 g) obtenido en el punto anterior (1) se disolvió en una mezcla (16 ml) de tetrahidrofurano-metanol (3:1), y se agregó una solución acuosa de hidróxido de litio 1 N (8.3 ml). La mezcla se agitó a temperatura ambiente durante 30 minutos y se acidificó con solución acuosa de ácido nítrico al 10 %. La solución se concentró a presión reducida y el material de goma precipitado se extrae con acetato de etilo (50 ml). La capa de acetato de etilo se lavó con salmuera saturada (30 ml), y se secó (Na₂SO₄). El acetato de etilo se evaporó a presión reducida para obtener el compuesto que figura en el título (1.36 g).

IR ν (neta) cm⁻¹: 2939, 2930, 2872, 1738, 1681, 1620, 1583, 1533, 1506

¹H-NMR(CDCl₃) δ (ppm): 0.92 (4H, d, J=6 Hz), 1.40-2.00 (1H, m), 1.84 (3H, d, J=4 Hz), 2.09 (2H, t, J=7 Hz), 2.23 (2H, s), 2.70 (2H, t, J=6 Hz), 2.93-3.40 (2H, m).

Ejemplo 21

7-(2-[2-(trans-2-ciclopentilvinil)-5-metiloxazol-4-il]etil)metansulfonato-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo

(1) Se disolvieron 2-ter-butoxicarbonil-7-hidroxi-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (2.83 g) y 2-[2-(trans-2-ciclopentilvinil)-5-metiloxazol-4-il]etilmetansulfonato (4.29 g) en tolueno (90 ml), y se agregaron carbonato de potasio (3.95 g) e hidrato de cloruro de tetraetilammonio (6.75 g). La mezcla se agitó a 90° C durante 16 horas. A la mezcla de reacción se agregó acetato de etilo (30 ml), y la mezcla se lavó sucesivamente con agua (50 ml) y salmuera saturada (50 ml), y se secó (Na₂SO₄). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener 2-ter-butoxicarbonil-7-(2-[2-(trans-2-ciclopentilvinil)-5-metiloxazol-4-il]oxazol-4-il)etil-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de metilo (3.9 g).

IR ν (neta) cm⁻¹: 2933, 2970, 1742, 1699, 1614 1533 1506

4.00 (2H, t, J=6 Hz), 4.30-5.40 (2H, m), 5.91-7.55 (8H, m)

Ejemplo 22

2-[2,4-benedioxolil]-7-(2-[2-metil-2-(4-metil-pentano-1-il)oxazol-4-il]etil)-1,2,3,4-tetrahidroisquinolin-(3H)-carbonilato de ter-butilammonio

El compuesto (1.22 g) obtenido en el ejemplo 19 se disolvió en metanol (7.0 ml), y se agregó ter-butilammonio (0.85 ml) por goteo. Se adicionó éter diisopropílico (70 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Los cristales precipitados se recogieron por filtración para obtener el compuesto que figura en el título (1.15 g).

IR ν (neta) cm⁻¹: 2741, 2933, 2944, 1683, 1620 1530, 1506

¹H-NMR(CDCl₃) δ (ppm): 0.93 (4H, d, J=6 Hz), 0.99 (9H, s), 1.60-2.00 (4H, m), 2.10 (2H, t, J=6 Hz), 2.20 (2H, s), 2.86 (2H, t, J=6 Hz), 2.90-3.40 (2H, m), 4.11 (2H, t, J=6 Hz), 4.30-5.25 (2H, m), 6.00-7.50 (12H, m)

¹H-NMR(CDCl₃) δ (ppm): 1.20-2.00 (17H, m), 2.27 (2H, s), 2.34-2.74 (1H, m), 2.80 (2H, t, J=6 Hz), 2.99-3.30 (2H, m), 3.61 (2H, s), 4.12 (2H, t, J=6 Hz), 4.24-5.20 (2H, m), 6.18 (1H, d, J=10 Hz), 6.61 (1H, dd, J=10 Hz, 7.5 Hz), 6.82-6.90 (2H, m), 7.01 (1H, d, J=8 Hz)

(2) El compuesto (3.89 g) obtenido en el punto anterior (1) se disolvió en ácido fórmico (9.7 ml) y se agregó una solución de cloruro de hidrógeno-2-propanol 10 N (2.30 ml) bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 15 minutos y la mezcla de reacción se vertió en una mezcla (200 ml) de éter diisopropílico - n-hexano (1:1) bajo enfriamiento con hielo. El aceite resultante se separó por decantación y se disolvió en acetato de etilo (100 ml). Se agregó agua (100 ml), y se neutralizó con bicarbonato de sodio. Se separaron las dos capas, y la capa de acetato de etilo se lavó sucesivamente con agua y salmuera saturada (50 ml cada una), y se secó (Na₂SO₄). El acetato de etilo se evaporó a presión reducida para obtener el compuesto que figura en el título (3.07 g).

IR ν (neta) cm⁻¹: 3344, 2931, 2970, 2777, 2740, 1639, 1643, 1612, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.20-1.97 (8H, m), 1.99 (1H, s), 2.27 (3H, s), 2.30-2.77 (1H, m), 2.86 (2H, t, J=6.7 Hz), 2.90-3.10 (2H, m), 3.60-3.83 (1H, m), 3.76 (3H, s), 3.95-4.34 (4H, m), 6.15 (1H, d, J=16.5 Hz), 6.51-6.80 (3H, m), 6.99 (1H, d, J=6.4 Hz)

Ejemplo 21

7-(2-(2-(trans-2-ciclopentilvinil)-5-metiloxazol-4-il)etil)-2-(2,4-benzodioxol)-1,2,3,4-tetrahidroisquinolina-(3H)-carbonilato de ter-butilamina

(1) El compuesto (3.05 g) obtenido en el ejemplo 21 se disolvió en cloruro de metileno (30 ml), y se agregaron cloruro de ácido cítrico (1.12 g) y trietilamina (1.25 ml) bajo enfriamiento con hielo. La mezcla se agitó a la misma temperatura durante 20 minutos. La mezcla de reacción se lavó con solución acuosa de ácido cítrico al 10 % y salmuera saturada (cada una 20 ml), y se secó (Na_2SO_4). Se evaporó el cloruro de metileno a presión reducida, y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener 7-(2-(2-(trans-2-ciclopentilvinil)-5-metiloxazol-4-il)etil)-2-(2,4-benzodioxol)-1,2,3,4-tetrahidroisquinolina-(3H)-carbonilato de metilo (2.49 g)

por filtración para obtener el compuesto que figura en el título (2.41 g)

IR v (NaJol) cm^{-1} : 2731, 2631, 2544 1633, 1626, 1523, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.99 (9H, s), 1.20-2.05 (11H, m), 2.27 (3H, s), 2.30-2.73 (1H, m), 2.85 (2H, t, J=6.5 Hz), 2.90-3.40 (2H, m), 4.10 (2H, t, J=6.5 Hz), 4.26-5.20 (3H, m), 5.94-7.30 (12H, m)

Ejemplo 22

2-(2-(heptanol)-7-(2-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etil)-1,2,3,4-tetrahidroisquinolina-(3H)-carbonilato de metilo

IR v (NaJol) cm^{-1} : 2955 2926, 2872, 1740, 1661, 1622, 1533, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.79-2.15 (3H, m), 0.94 (9H, d, J=6.4 Hz), 1.20-2.00 (9H, m), 2.20-2.45 (2H, m), 2.31 (3H, t, J=6.0 Hz), 2.28 (3H, s), 2.87 (2H, t, J=6.8 Hz), 3.00-3.35 (2H, m), 3.60 (3H, s), 4.15 (2H, t, J=6.8 Hz), 4.40-5.00 (3H, m), 6.16 (1H, d, J=16.0 Hz), 6.35-7.20 (8H, m)

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IR v (nato) cm^{-1} : 3464, 2953, 2870, 1740, 1657, 1628 1603, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.20-1.97 (9H, m), 1.03 (3H, d, J=6.4 Hz), 2.27 (3H, s), 2.40-2.75 (1H, m), 2.86 (2H, t, J=6.5 Hz), 3.00-3.22 (2H, m), 3.59 (3H, s), 4.14 (2H, t, J=6.5 Hz), 4.36-5.00 (2H, m), 5.40-5.60 (1H, m), 6.07-6.80 (8H, m), 6.15 (1H, d, J=16.1 Hz), 6.51 (1H, dd, J=16.1, 7.2 Hz), 7.02 (1H, d, J=6.4 Hz), 7.13-7.30 (1H, m)

(2) El compuesto (2.48 g) obtenido en el punto anterior (1) se disolvió en una mezcla (60 ml) de tetrahidrofurano-metanol (3:1), y se agregó una solución acuosa de hidróxido de litio 1 N (14.7 ml). La mezcla se agitó a temperatura ambiente durante 80 minutos y se acidificó con ácido clorhídrico 6 N. La solución se concentró a presión reducida y el material de goma precipitado se extrajo con acetato de etilo (30 ml). La capa de acetato de etilo se lavó con salmuera saturada (20 ml), y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se disolvió en metanol (2.4 ml). Tras la adición por gotas de ter-butilamina (1.0 ml), se agregó éter diisopropílico (30 ml), y la mezcla se agitó bajo enfriamiento con hielo durante 1 hora 20 minutos. Los cristales precipitados se recogieron

Ejemplo 24

2-(2-(heptanol)-7-(2-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etil)-1,2,3,4-tetrahidroisquinolina-(3H)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 1661, 1616, 1539, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.75-2.20 (3H, m), 0.93 (9H, d, J=6.4 Hz), 1.02 (3H, s), 1.20-1.60 (4H, m), 1.60-1.95 (1H, m), 1.95-2.30 (2H, m), 3.10 (2H, t, J=6.8 Hz), 2.28 (3H, s), 2.86 (2H, t, J=6.8 Hz), 3.00-3.40 (2H, m), 4.10 (2H, t, J=6.8 Hz), 4.40-5.20 (3H, m), 6.15 (1H, d, J=16.1 Hz), 6.10-7.20 (9H, m)

Ejemplo 25

7-(2-(2-(trans-1-hexano-1-il)-3-metiloxazol-4-il)etil)-1,2,3,4-tetrahidroisquinolina-(3H)-carbonilato de metilo

IR v (nato) cm^{-1} : 3248, 2935, 2829, 2872, 1742, 1661, 1613 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.72-1.06 (3H, m), 1.06-1.65 (4H, m), 1.96-2.40 (3H, m), 2.27 (3H, s), 2.88-3.02 (2H, m), 3.84 (3H, t, J=6.7 Hz), 3.97-3.74 (1H, m), 3.76 (3H, m)

m), 3.91-4.10 (2H, m), 4.14 (2H, t, J=6.7 Hz), 6.16 (1H, d, J=16.0 Hz), 6.30-6.70 (2H, m), 6.80 (1H, d, J=7.8 Hz)

Exemplo 36

2-(2,4-bisoxolanil)-7-(2-(2-(trans-1-hexen-1-il)-5-metiloxazol-4-il)etil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR ν (nato) cm^{-1} : 3400, 3020, 2957, 2936, 2872, 1740, 1657, 1639, 1600, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.78-1.07 (3H, m), 1.20-1.60 (4H, m), 1.66 (3H, d, J=5.0 Hz), 2.00-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.6 Hz), 3.00-3.25 (2H, m), 3.60 (3H, s), 4.18 (2H, t, J=6.6 Hz), 4.35-5.10 (2H, m), 6.59 (1H, br-s), 6.96-6.94 (7H, m), 7.81 (1H, d, J=6.4 Hz), 7.13-7.80 (1H, m)

Exemplo 37

2-(2,4-bisoxolanil)-7-(2-(2-(trans-1-hexen-1-il)-5-metiloxazol-4-il)etil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de ter-butilmina

Exemplo 38

2-(2,4-bisoxolanil)-7-(2-(3-metil-2-(5-metil-trans-1-hexen-1-il)oxazol-4-il)etil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR ν (nato) cm^{-1} : 3462, 2953, 2938, 2870, 1740, 1653, 1630, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.90 (6H, d, J=6.3 Hz), 1.14-1.72 (3H, m), 1.86 (3H, d, J=5.0 Hz), 2.08-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.6 Hz), 3.00-3.25 (2H, m), 3.60 (3H, s), 4.18 (2H, t, J=6.6 Hz), 4.39-5.20 (2H, m), 5.42-5.65 (1H, m), 6.00-6.87 (7H, m), 7.04 (1H, d, J=6.1 Hz), 7.16-7.51 (1H, m)

Exemplo 39

2-(2,4-bisoxolanil)-7-(2-(3-metil-2-(5-metil-trans-1-hexen-1-il)oxazol-4-il)etil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de ter-butilmina

IR ν (NaJol) cm^{-1} : 3400, 2735, 2835, 2550, 1657, 1634, 1650, 1506

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IR ν (NaJol) cm^{-1} : 3400, 2743, 2837, 2548, 2220, 1651, 1620, 1534, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.75-1.10 (3H, m), 0.98 (6H, s), 1.20-1.60 (4H, m), 1.70-2.00 (3H, m), 2.07-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.5 Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6.5 Hz), 4.25-5.20 (3H, m), 5.90-7.40 (12H, m)

Exemplo 40

7-(2-(2-metil-2-(5-metil-trans-1-hexen-1-il)oxazol-4-il)etil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR ν (nato) cm^{-1} : 3346, 2953, 2936, 2870, 2840, 1742, 1641, 1613, 1533, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.90 (6H, d, J=6.1 Hz), 1.13-1.73 (3H, m), 1.86 (1H, br-s), 2.04-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.6 Hz), 2.90-3.00 (2H, m), 3.55-3.73 (1H, m), 3.77 (3H, s), 3.90-4.10 (2H, m), 4.22 (2H, t, J=6.6 Hz), 6.17 (1H, d, J=16.0 Hz), 6.39-6.91 (3H, m), 6.99 (1H, d, J=6.3 Hz)

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.90 (6H, d, J=6.3 Hz), 0.97 (6H, s), 1.20-1.70 (3H, m), 1.70-1.90 (3H, m), 2.06-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.4 Hz), 2.90-3.25 (3H, m), 4.10 (2H, t, J=6.4 Hz), 4.25-5.20 (3H, m), 5.72-7.30 (12H, m)

Exemplo 41

7-(2-(2-metil-2-(1-metil-trans-1-penten-1-il)oxazol-4-il)etil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR ν (nato) cm^{-1} : 3344, 2957, 2930, 2872, 1742, 1647, 1612, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.95 (3H, t, J=7.2 Hz), 1.20-1.72 (2H, m), 2.02 (3H, s), 2.03-2.30 (3H, m), 2.27 (3H, s), 2.88 (2H, t, J=6.8 Hz), 2.90-3.10 (2H, m), 3.60-3.80 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.14 (2H, t, J=6.6 Hz), 6.30-6.90 (3H, m), 6.99 (1H, d, J=6.4 Hz)

Exemplo 42

2-(2,4-bisoxolanil)-7-(2-(3-metil-2-(1-metil-trans-1-penten-1-il)oxazol-4-il)etil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR ν (nato) cm^{-1} : 3462, 2937, 2930, 2872, 1740, 1635, 1620, 1612, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.68 (3H, t, J=7.0Hz), 1.20-1.75 (2H, m), 1.68 (3H, d, J=5.0Hz), 2.00-2.30 (2H, m), 2.04 (3H, s), 2.28 (3H, m), 2.89 (2H, t, J=6.5Hz), 3.02-3.25 (3H, m), 3.60 (3H, s), 4.18 (2H, t, J=6.5Hz), 4.36-5.00 (2H, m), 5.80 (1H, br-t), 5.82-6.03 (2H, m), 7.03 (1H, d, J=6.1Hz), 7.18-7.53 (1H, m)

Exemple 22

2-(2,4-bisoxolanil)-7-(2-(5-metil-2-(1-metil-trans-1-penten-1-il)oxazol-4-il)etanol)-1,2,3,4-tetrahidroquinolin-(3H)-carboxilato de ter-butillina

IR ν (Nujol) cm^{-1} : 3748, 2937, 2844, 2220, 1681, 1624, 1600, 1583

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.80-1.00 (3H, m), 0.97 (3H, s), 1.11-1.70 (2H, m), 1.70-1.93 (3H, m), 1.93-2.35 (2H, m), 2.01 (3H, s), 2.27 (3H, s), 2.67 (2H, t, J=6.7Hz), 2.80-3.40 (3H, m), 4.10 (3H, t, J=6.7Hz), 4.24-5.20 (3H, m), 5.92-7.38 (11H, m)

(2H, t, J=6.4 Hz), 4.30-5.08 (3H, m), 7.03 (1H, d, J=6.4Hz), 5.80-7.00 (7H, m)

Exemple 23

2-(2,4-bisoxolanil)-7-(2-(3-metil-2-(1-metil-trans-1-buten-1-il)oxazol-4-il)etanol)-1,2,3,4-tetrahidroquinolin-(3H)-carboxilato de ter-butillina

IR ν (Nujol) cm^{-1} : 2733, 2635, 2650, 1637, 1634, 1611, 1536, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.99 (3H, s), 1.05 (3H, t, J=7.5Hz), 1.68-1.98 (3H, m), 2.01 (3H, s), 2.03-2.45 (2H, m), 2.28 (3H, s), 2.67 (2H, t, J=6.7Hz), 2.80-3.36 (2H, m), 4.11 (2H, t, J=6.7Hz), 4.23-5.20 (3H, m), 5.90-6.30 (12H, m)

Exemple 27

Acido 7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etanol)-2-(2,2,3,3,3-pentafluoropropionil)-1,2,3,4-tetrahidroquinolin-(3H)-carboxilic

IR ν (Nujol) cm^{-1} : 2723, 2809, 1917, 1732, 1682, 1614, 1569, 1531

Exemple 24

7-(2-(2-metil-2-(1-metil-trans-1-buten-1-il)oxazol-4-il)etanol)-1,2,3,4-tetrahidroquinolin-(3H)-carboxilato de metilo

IR ν (nato) cm^{-1} : 2936, 2832, 2873, 1739, 1646, 1611, 1592, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.06 (3H, t, J=7.5Hz), 2.01 (3H, s), 2.10-2.45 (3H, m), 2.27 (3H, s), 2.70-3.20 (4H, m), 2.80-3.90 (1H, m), 3.76 (3H, s), 4.05 (2H, s), 4.14 (2H, t, J=6.0Hz), 4.23-4.65 (3H, m), 5.99 (1H, d, J=6.0Hz)

Exemple 25

2-(2,4-bisoxolanil)-7-(2-(3-metil-2-(1-metil-trans-1-buten-1-il)oxazol-4-il)etanol)-1,2,3,4-tetrahidroquinolin-(3H)-carboxilato de metilo

IR ν (nato) cm^{-1} : 2961, 2933, 2875, 1739, 1638, 1627, 1606, 1534, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.06 (3H, t, J=7.5Hz), 1.08 (3H, d, J=5.0Hz), 2.01 (3H, s), 2.03-2.45 (3H, m), 2.20 (3H, s), 2.88 (3H, t, J=6.4 Hz), 3.00-3.40 (2H, m), 4.15

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.93 (3H, t, J=7.1Hz), 1.20-1.70 (2H, m), 2.00-2.30 (2H, m), 2.23 (3H, s), 2.50-2.87 (2H, m), 2.91-3.32 (2H, m), 3.64-4.00 (2H, m), 4.21-5.03 (2H, m), 5.03-5.47 (1H, m), 6.10 (1H, d, J=16.3Hz), 6.42-6.88 (3H, m), 7.05 (1H, d, J=6.4Hz), 7.14-7.60 (1H, br)

Exemple 26

7-(2-(2-(trans-2-ciclohexilvinil)-5-metiloxazol-4-il)etanol)-1,2,3,4-tetrahidroquinolin-(3H)-carboxilato de metilo

IR ν (nato) cm^{-1} : 2926, 2851, 1740, 1641, 1612, 1582, 1533, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.80-2.45 (11H, m), 2.27 (3H, s), 2.70-3.20 (2H, m), 2.80 (2H, t, J=7.0Hz), 3.33-3.83 (1H, m), 3.76 (3H, s), 4.04 (2H, s), 4.14 (2H, t, J=6.0Hz), 6.12 (1H, d, J=16.0Hz), 6.40-6.80 (3H, m), 6.99 (1H, d, J=6.4Hz)

Exemple 28

7-(2-(2-(trans-2-ciclotetrasilil)-5-metiloxazol-4-il)etoxi)-2-(2,4-benzodioxoli)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilato de metila

IR v (NaJol) cm^{-1} : 1745, 1614, 1531, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.65-2.45 (14H, m), 2.27 (3H, s), 2.67 (2H, t, J=4 Hz), 2.90-3.25 (2H, m), 3.56 (3H, s), 4.15 (2H, t, J=6 Hz), 4.30-5.05 (3H, m), 6.00-7.55 (7H, m), 6.50 (1H, d, J=6 Hz), 7.03 (1H, d, J=6.4Hz)

Exemplo 40

7-(2-(2-(trans-2-ciclotetrasilil)-5-metiloxazol-4-il)etoxi)-2-(2,4-benzodioxoli)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2739, 2633, 2549, 1655, 1630, 1500, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.98 (9H, s), 1.00-2.40 (14H, m), 2.27 (3H, s), 2.95 (2H, t, J=6.0Hz), 2.90-3.30 (2H, m), 4.10 (2H, t, J=6 Hz), 4.20-5.20 (3H, m), 5.80-7.45 (12H, m)

Exemplo 41

Exemplo 42

7-(2-(2-(2,2-dimetil-trans-1-penten-1-il)-5-metiloxazol-4-il)etoxi)-2-(2,4-benzodioxoli)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2506, 2745, 2637 2216, 1653, 1593

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.97 (12H, s), 1.00-2.00 (3H, m), 2.28 (3H, s), 2.86 (2H, t, J=6 Hz), 2.90-3.35 (2H, m), 4.11 (2H, t, J=6 Hz), 4.28-5.20 (3H, m), 5.90-7.40 (12H, m).

Exemplo 43

7-(2-(2-(2,2-dimetil-trans-1-penten-1-il)-5-metiloxazol-4-il)etoxi)-2-(2,4-benzodioxoli)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 3400, 2749, 2635, 2544, 2220, 1651, 1632, 1553

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.92 (3H, t, J=7 Hz), 0.99 (9H, s), 1.05 (6H, s), 1.41 (2H, q, J=7 Hz), 1.63-1.94

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Acido 2-cincoxi-7-(2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilico

IR v (NaJol) cm^{-1} : 1726, 1647, 1612, 1576, 1533, 1506

$^1\text{H-NMR}(\text{DMSO}-d_6)$ δ (ppm): 0.69 (3H, t, J=7 Hz), 1.20-1.70 (2H, m), 1.95-2.25 (2H, m), 2.20 (3H, s), 2.45-2.95 (2H, m), 2.95-3.15 (2H, m), 3.40-5.00 (1H, br), 3.95-4.35 (2H, m), 4.40-5.80 (3H, m), 6.10 (1H, d, J=10 Hz), 6.35-6.90 (2H, m), 7.11 (1H, d, J=6 Hz), 7.30-7.95 (7H, m)

Exemplo 42

7-(2-(2-(2-etil-trans-1-penten-1-il)-5-metiloxazol-4-il)etoxi)-2-(2,4-benzodioxoli)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2735, 2633, 2544, 1653, 1624, 1599, 1551, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.97 (6H, t, J=7 Hz), 0.94 (3H, s), 1.20-1.63 (4H, m), 1.63-2.10 (4H, m), 2.28 (3H, s), 2.56 (2H, t, J=6 Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6 Hz), 4.40-5.30 (3H, m), 5.80-7.60 (12H, m)

(2H, m), 2.20 (3H, s), 2.86 (2H, t, J=6 Hz), 2.90-3.37 (2H, m), 4.11 (2H, t, J=6 Hz), 4.23-5.20 (3H, m), 6.09 (1H, d, J=16 Hz), 6.00-7.39 (12H, m)

Exemplo 45

7-(2-(2-(4,4-dimetil-trans-1-penten-1-il)-5-metiloxazol-4-il)etoxi)-2-(2,4-benzodioxoli)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2733, 2635, 2559, 1687, 1634, 1611, 1599, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.94 (9H, s), 1.01 (6H, s), 1.65-1.98 (2H, m), 2.09 (2H, d, J=7 Hz), 2.20 (3H, s), 2.86 (2H, t, J=6 Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6 Hz), 4.25-5.20 (3H, m), 5.90-7.35 (12H, m)

Exemplo 46

2-(2,4-benzodioxoli)-7-(2-(5-metil-2-(3-metil-trans-1-buten-1-il)oxazol-4-il)etoxi)-1,2,3,4-tetrahidropirimidina-(2H)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2741, 2639, 2544, 1651, 1622, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.01 (3H, s), 1.00 (3H, d, J=6.7 Hz), 1.43-1.46 (2H, m), 1.26 (2H, s), 2.35-2.70 (1H, m), 3.06 (2H, t, J=6.0 Hz), 2.89-3.30 (2H, m), 4.11 (2H, t, J=6.0 Hz), 4.23-5.20 (2H, m), 5.83-6.00 (12H, m)

Exemplo 47

2-(2-metil-2-pentanol)-7-(2-(2-metil-2-(trans-1-penten-1-il)oxazol-4-il)oxol-1,2,3,4-tetrahidroquinolin-3il)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 3390, 2741, 2635, 2846, 1661, 1614, 1585

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.70-1.14 (10H, m), 1.14-2.30 (7H, m), 2.27 (2H, s), 2.85 (2H, br-t), 2.90-3.40 (2H, m), 4.10 (2H, br-t), 4.40-6.20 (2H, m), 5.80-7.10 (10H, m)

Exemplo 48

2-(4,4-dimetil-2-pentanol)-7-(2-(2-metil-2-(trans-1-penten-1-il)oxazol-4-il)oxol-1,2,3,4-tetrahidroquinolin-3il)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2741, 2633, 1622, 1586, 1504

IR v (NaJol) cm^{-1} : 2971, 1732, 1697, 1614, 1503, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.91 (3H, br-t), 1.10-1.70 (4H, m), 2.02 (2H, t, J=6.0 Hz), 1.90-2.40 (2H, m), 2.29 (2H, s), 2.95-3.40 (3H, m), 4.07 (2H, t, J=6.0 Hz), 4.20-5.85 (2H, m), 6.28 (1H, d, J=16.2 Hz), 6.80-6.85 (4H, m), 7.04 (1H, d, J=7.7 Hz), 7.20-7.63 (2H, m)

Exemplo 51

2-(2,4-hexadienol)-7-(2-(2-(trans-1-penten-1-il)-5-pentoxiloxazol-4-il)oxol-1,2,3,4-tetrahidroquinolin-3il)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2731, 2633, 2846, 1630, 1553, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.91 (3H, t, J=7.0 Hz), 0.96 (3H, s), 1.25-2.00 (7H, m), 2.20 (2H, q, J=7.0 Hz), 2.40 (2H, t, J=7.0 Hz), 2.67 (2H, t, J=6.0 Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6.0 Hz), 4.23-5.20 (2H, m), 5.90-7.00 (12H, m)

Exemplo 52

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.94 (3H, t, J=7.0 Hz), 1.05 (3H, s), 1.10 (3H, s), 1.20-1.70 (2H, m), 2.00-2.45 (2H, m), 2.28 (2H, s), 2.36 (2H, t, J=6.0 Hz), 2.90-3.30 (2H, m), 4.11 (2H, t, J=6.0 Hz), 4.20-5.80 (2H, m), 5.80-6.80 (2H, br), 6.00-7.20 (7H, m)

Exemplo 53

2-(2,4-hexadienol)-7-(2-(2-metil-2-(trans-2-tiofen-2-ilvinil)oxazol-4-il)oxol-1,2,3,4-tetrahidroquinolin-3il)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 3420, 2737, 2633, 2846, 1491, 1422, 1550, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.97 (3H, s), 1.03 (2H, br-d), 2.21 (3H, s), 2.89 (2H, t, J=6.0 Hz), 2.90-3.23 (2H, m), 4.13 (2H, t, J=6.0 Hz), 4.20-5.20 (2H, m), 6.00-6.70 (10H, m), 6.85-7.27 (2H, m), 7.40 (1H, d, J=16.4 Hz)

Exemplo 54

Ácido 2-(2-butanol)-7-(2-(2-metil-2-(etil)oxiloxazol-4-il)oxol-1,2,3,4-tetrahidroquinolin-3il)-carbonilico

2-(2,2-difluorbutiril)-7-(2-(2-metil-2-(trans-1-penten-1-il)oxazol-4-il)oxol-1,2,3,4-tetrahidroquinolin-3il)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 2749, 2639, 2532, 1661, 1614, 1564, 1500

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.75-2.20 (6H, m), 1.23-1.70 (2H, m), 1.65-2.45 (4H, m), 0.93 (3H, s), 1.20-2.70 (11H, m), 2.27 (3H, s), 2.85 (2H, t, J=6.0 Hz), 2.90-3.28 (2H, m), 4.11 (2H, t, J=6.0 Hz), 4.20-5.15 (2H, m), 6.17 (1H, d, J=16.3 Hz), 6.25-7.80 (7H, m)

Exemplo 55

2-(4,4-difluorpentanol)-7-(2-(2-metil-2-(trans-1-penten-1-il)oxazol-4-il)oxol-1,2,3,4-tetrahidroquinolin-3il)-carbonilato de ter-butilamina

IR v (NaJol) cm^{-1} : 3390, 2749, 2637, 2830, 1646, 1554

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.95 (3H, t, J=7.5 Hz), 0.90 (3H, s), 1.26-2.70 (11H, m), 2.20 (3H, s), 2.80 (2H, br-t), 3.00-3.41 (2H, m), 4.11 (2H, br-t), 4.20-6.70 (2H, m), 4.80-5.10 (1H, m), 5.57-6.14 (3H, br), 6.15 (1H, d, J=16.3 Hz), 6.41-6.80 (3H, m), 6.83-7.00 (1H, m)

Ejemplo 24

Ácido 7-(2-[5-metil-2-(trans-1-penten-1-il)enonil-4-il]etenil)-2-(4-pentenil)-1,2,3,4-tetrahidroisocuinolina-(3H)-carbonílico

IR v (KBr) cm^{-1} : 2723, 2821, 1732, 1661, 1614, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.99 (2H, t, J=7.8Hz), 1.20-1.75 (2H, m), 2.23 (2H, t, J=6.8Hz), 2.34 (2H, m), 2.94 (2H, br-t), 3.00-3.09 (4H, m), 4.09 (2H, br-t), 4.30-5.30 (2H, m), 6.36 (1H, d, J=16.0Hz), 7.04 (1H, d, J=7.7Hz), 8.50-8.96 (2H, m), 9.83 (1H, br-s).

Ejemplo 25

2-(2,4-bisoxepil)-7-(2-[5-metil-4-(2-metiloxietil)enonil-4-il]etenil)-1,2,3,4-tetrahidroisocuinolina-(3H)-carbonilato de ter-butilamina

IR v (KBr) cm^{-1} : 2743, 2837, 2846, 1681, 1634, 1601, 1553, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.97 (9H, s), 1.03-2.00 (2H, m), 2.11 (2H, s), 2.25 (2H, s), 2.70-3.40 (6H, m), 2.88

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.99 (2H, s), 1.14 (2H, s), 1.30-2.05 (1H, m), 2.20 (2H, s), 2.84 (2H, t, J=6.8Hz), 2.90-3.40 (2H, m), 4.11 (2H, t, J=6.8Hz), 4.25-5.30 (2H, m), 5.80-7.45 (12H, m)

Ejemplo 26

Ácido 7-(2-[5-metil-2-(4-metil-trans-1-penten-1-il)enonil-4-il]etenil)-2-(4-pentenil)-1,2,3,4-tetrahidroisocuinolina-(3H)-carbonílico

(1) Se disolvió 7-(2-[5-metil-2-(4-metil-trans-1-penten-1-il)enonil-4-il]etenil)-1,2,3,4-tetrahidroisocuinolina-(3H)-carbonilato de metilo (1,5 g) en N,N-dimetilformamida (10 ml), y se agregaron trietilamina (1,4 ml) y 5-bromo-1-penteno (1,2 ml). La mezcla se agitó a temperatura ambiente durante 48 horas, y se agregaron trietilamina (1,05 ml) y 5-bromo-1-penteno (0,89 ml). La mezcla se agitó luego durante 24 horas. Se agregó acetato de etilo (20 ml), y la mezcla se lavó dos veces con agua (50 ml), solución acuosa de ácido cítrico al 10 % y salmuera saturada (10 ml cada uno), y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna de gel de sílice para obtener 7-(2-[5-metil-2-(4-metil-trans-1-penten-1-il)enonil-4-il]etenil)-2-(4-pentenil)-1,2,3,4-

(2H, t, J=6.8Hz), 4.10 (2H, t, J=6.8Hz), 4.25-5.30 (2H, m), 5.80-7.40 (12H, m)

Ejemplo 26

2-(2,4-bisoxepil)-7-(2-[5-metil-2-(2-trans-1-metiloxietil)enonil-4-il]vinil)enonil-4-il]etenil)-1,2,3,4-tetrahidroisocuinolina-(3H)-carbonilato de ter-butilamina

IR v (KBr) cm^{-1} : 2739, 2831, 2846, 1631, 1622, 1599, 1505, 1347, 1505

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.97 (9H, s), 1.05 (2H, s), 1.15-2.00 (12H, m), 2.20 (2H, s), 2.84 (2H, t, J=6.8Hz), 2.90-3.40 (2H, m), 4.11 (2H, t, J=6.8Hz), 4.25-5.30 (2H, m), 5.80-7.30 (12H, m)

Ejemplo 27

2-(2,4-bisoxepil)-7-(2-[5-metil-2-(2-trans-1-metiloxietil)enonil-4-il]vinil)enonil-4-il]etenil)-1,2,3,4-tetrahidroisocuinolina-(3H)-carbonilato de ter-butilamina

IR v (KBr) cm^{-1} : 2739, 2833, 2846, 1634, 1599, 1504

tetrahidroisocuinolina-(3H)-carbonilato de metilo como un aceite (0,89 g)

IR v (nato) cm^{-1} : 3449, 2953, 2928, 2876, 1735, 1641, 1614, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.94 (6H, d, J=6.3Hz), 1.40-1.90 (2H, m), 1.90-2.33 (4H, m), 2.27 (2H, s), 2.50-3.17 (6H, m), 3.03 (2H, s), 3.70-4.25 (2H, m), 4.80-5.13 (2H, m), 5.45-6.00 (1H, m), 6.16 (1H, d, J=16.0Hz), 6.36-6.79 (2H, m), 6.97 (1H, d, J=6.4Hz)

(2) El compuesto (0,8 g) obtenido en el punto anterior (1) se disolvió en una mezcla (23 ml) de tetrahidrofuran-metanol (3:1), y se agregó una solución acuosa de hidróxido de litio 1 N (5,66 ml). La mezcla se agitó durante a temperatura ambiente 40 minutos y se acidificó con solución acuosa de ácido cítrico al 10 %. La solución se concentró a presión reducida y el material de goma precipitado se extrajo con acetato de etilo (20 ml). La capa de acetato de etilo se lavó con salmuera saturada (20 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y n-hexano se agregó al residuo. Las cristales precipitados se recogieron por filtración para obtener el compuesto que figura en el título (0,74 g)

IR v (Nujol) cm^{-1} : 3400, 3037, 2725, 2664, 2543, 2494, 1626, 1551, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.92 (6H, d, J=6.4 Hz), 1.40-2.30 (7H, m), 2.20 (3H, s), 2.60-3.33 (8H, m), 3.72 (1H, br-t), 3.82-4.46 (4H, m), 4.80-5.20 (2H, m), 5.42-5.97 (1H, m), 6.15 (1H, d, J=16.1 Hz), 6.40-6.90 (2H, m), 7.06 (1H, d, J=6.4 Hz), 8.53-8.65 (1H, br)

Ejemplo 52

Ácido 2-bencil-7-(2-(3-metil-2-(4-metil-trans-1-penten-1-yl)oxazol-4-yl)etil)oxazolidin-3(2H)-carbonílico

(1) Se disolvieron 2-bencil-7-hidroxi-1,2,3,4-tetrahidrooxazolin-3(2H)-carbonílico de metilo (483 mg) y 2-(3-metil-2-(4-metil-trans-1-penten-1-yl)oxazol-4-yl)etil)oxazolidin-3(2H)-carbonílico (700 mg) en tolueno (15 ml), y se agregaron carbonato de potasio (674 mg) e hidrato de fluoruro de tetraetilamonio (106 mg). La mezcla se agitó a 90° C durante 18 horas. A la mezcla de reacción se agregó acetato de etilo (10 ml), y la mezcla se lavó sucesivamente con agua (20 ml) y salmuera saturada (20 ml), y se secó (Na_2SO_4). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna

de gel de sílice para obtener 2-bencil-7-(2-(3-metil-2-(4-metil-trans-1-penten-1-yl)oxazol-4-yl)etil)oxazolidin-3(2H)-carbonílico de metilo (590 mg)

IR v (sota) cm^{-1} : 3443, 3037, 2983, 2926, 2871, 2841, 1731, 1613, 1534, 1505

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.93 (6H, d, J=6.4 Hz), 1.40-2.00 (1H, m), 2.10 (2H, t, J=6.8 Hz), 2.26 (3H, s), 2.84 (2H, t, J=6.8 Hz), 3.06 (2H, d, J=6.6 Hz), 3.66 (3H, s), 3.70-4.30 (5H, m), 3.90 (2H, s), 6.15 (1H, d, J=16.1 Hz), 6.30-6.70 (3H, m), 6.90 (1H, d, J=6.2 Hz), 7.16-7.50 (5H, m).

(2) El compuesto de (1) (576 mg) obtenido en el punto anterior (1) se disolvió en una mezcla (16 ml) de tetrahidrofurano-metanol (3:1), y se agregó una solución acuosa de hidruído de litio 1 M (3.5 ml). La mezcla se agitó a 40° C durante 1.5 horas y se acidificó con ácido clorhídrico 6 N. La solución se concentró a presión reducida y el material de goma precipitado se extrajo con acetato de etilo (15 ml). La capa de acetato de etilo se lavó con salmuera saturada (10 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y se agregó n-hexano al residuo obtenido. La mezcla se agitó bajo enfriamiento con hielo durante 30 minutos, y los cristales

precipitados se recogieron por filtración para obtener el compuesto que figura en el título (443 mg)

IR v (Nujol) cm^{-1} : 3385, 3047, 1716, 1636, 1585, 1549, 1533, 1501

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.93 (6H, d, J=6.4 Hz), 1.40-1.90 (1H, m), 2.10 (2H, t, J=6.7 Hz), 2.27 (3H, s), 2.83 (2H, t, J=6.8 Hz), 3.10 (2H, d, J=6.1 Hz), 3.82-4.40 (5H, m), 4.63 (2H, s), 6.15 (1H, d, J=15.6 Hz), 6.36-6.65 (3H, m), 7.06 (1H, d, J=6.6 Hz), 7.20-7.40 (5H, m), 8.37 (1H, br-s)

Ejemplo 53

Ácido 2-bencil-7-(2-(2-(3,3-dimetil-trans-1-penten-1-yl)-5-metiloxazol-4-yl)etil)oxazolidin-3(2H)-carbonílico

IR v (Nujol) cm^{-1} : 3420, 1680, 1614, 1506

$^1\text{H-NMR}(\text{DMSO}-d_6)$ δ (ppm): 1.67 (3H, s), 2.23 (3H, s), 2.77 (2H, t, J=6.3 Hz), 2.80-3.10 (2H, m), 3.20-4.60 (5H, m), 6.07 (1H, d, J=16.5 Hz), 6.50 (1H, d, J=16.5 Hz), 6.40-6.80 (2H, m), 7.01 (1H, J=6.4 Hz), 7.32 (5H, br-s)

Ejemplo 61

2-(2,3-dimetiloxopil)-7-(2-(3-metil-2-(4-metil-trans-1-penten-1-yl)oxazol-4-yl)etil)oxazolidin-3(2H)-carbonílico de tri-n-butilamina

IR v (Nujol) cm^{-1} : 3390, 2746, 2637, 2554, 1641, 1612, 1543

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.67 (6H, s), 0.93 (6H, d, J=6.6 Hz), 1.62 (6H, s), 1.40-2.00 (1H, m), 2.11 (2H, t, J=6.8 Hz), 2.28 (3H, s), 2.40 (2H, d, J=7.0 Hz), 2.60-3.20 (2H, m), 2.86 (2H, t, J=6.6 Hz), 3.20-3.33 (1H, m), 4.00 (2H, dd, J=16.6 Hz, 32.7 Hz), 4.11 (2H, t, J=6.6 Hz), 6.16 (1H, d, J=16.6 Hz), 6.37-7.00 (5H, m), 6.90 (1H, d, J=6.1 Hz)

Ejemplo 62

Ácido 7-(2-(3-metil-2-(trans-1-penten-1-yl)oxazol-4-yl)etil)-2-(2,2,3,3,3-pentafluoropropil)-1,2,3,4-tetrahidrooxazolin-3(2H)-carbonílico

IR v (Nujol) cm^{-1} : 1897, 1610, 1529, 1509

$^1\text{H-NMR}(\text{DMSO-}d_6)$ δ (ppm): 0.88 (3H, t, J=7 Hz), 1.20-1.70 (2H, m), 1.85-2.25 (2H, m), 2.25 (3H, s), 2.80-4.40 (1H, br), 2.79 (2H, m), 2.95-3.15 (2H, m), 3.30-4.40 (7H, m), 6.19 (1H, d, J=16 Hz), 6.33-6.90 (3H, m), 7.02 (1H, d, J=6 Hz)

Exemple 63

Acide 7-(2-(5-méthyl-2-(trans-1-penten-1-yl)oxazol-4-yl)éthyl)-2-(2,3,4-trifluorobenzoyl)-1,2,3,4-tétrahydroquinolin-3(2H)-carboxyle

IR v (KBr) cm^{-1} : 1616, 1606.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.93 (3H, t, J=6 Hz), 1.30-1.75 (2H, m), 2.10-2.70 (4H, m), 2.27 (3H, s), 2.75-3.40 (6H, m), 3.60-4.20 (2H, m), 5.00-5.00 (1H, br), 6.10-6.90 (4H, m), 7.02 (1H, d, J=6 Hz)

Exemple 64

Acide 2-(2-butyl)-7-(2-(5-méthyl-2-(4-méthyl-trans-1-penten-1-yl)oxazol-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-3(2H)-carboxyle

IR v (KBr) cm^{-1} : 3388, 3080, 2725, 2663, 1717, 1614, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.93 (3H, t, J=6 Hz), 1.40-1.99 (1H, m), 2.11 (2H, t, J=6 Hz), 2.25 (3H, s), 2.33-2.62 (2H, m), 2.70-3.35 (6H, m), 3.76 (1H, br-t), 3.89-4.46 (4H, m), 4.90-5.25 (2H, m), 5.45-5.94 (1H, m), 6.15 (1H, d, J=16 Hz), 6.40-6.90 (3H, m), 7.00 (1H, d, J=6 Hz), 8.60-9.00 (1H, br)

Exemple 65

2-(2,4-bis(méthyl)-7-(2-(2-méthyl-trans-1-penten-1-yl)-2-méthyl-oxazol-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-3(2H)-carboxyle de ter-butylamine

IR v (KBr) cm^{-1} : 2727, 1652, 1624, 1595, 1535, 1507, 1506.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.00 (9H, s), 1.02-2.00 (3H, m), 2.29 (2H, m), 2.87 (2H, t, J=6 Hz), 2.90-3.25 (2H, m), 3.38 (3H, s), 3.68-4.20 (2H, m), 4.11 (2H, t, J=6 Hz), 4.30-5.20 (3H, m), 5.90-6.40 (12H, m)

Exemple 66

7-(2-(2-(5-fluoro-trans-1-penten-1-yl)-5-méthyl-oxazol-4-yl)éthyl)-2-(2,4-bis(méthyl)-1,2,3,4-tétrahydroquinolin-3(2H)-carboxyle de ter-butylamine

IR v (KBr) cm^{-1} : 2736, 2631, 2544, 2432, 2365, 2212, 1681, 1624, 1599, 1533, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.99 (9H, s), 1.30-2.10 (3H, m), 2.15-2.55 (2H, m), 2.29 (3H, s), 2.80-3.40 (2H, m), 2.86 (2H, t, J=6 Hz), 4.11 (2H, t, J=6 Hz), 4.47 (2H, dt, J=47.0, 3.7 Hz), 4.80-5.20 (3H, m), 5.80-6.80 (6H, m), 6.85-7.25 (2H, m)

Exemple 67

7-(2-(2-cyclopentylidèneéthyl)-5-méthyl-oxazol-4-yl)éthyl)-2-(2,4-bis(méthyl)-1,2,3,4-tétrahydroquinolin-3(2H)-carboxyle de ter-butylamine

IR v (KBr) cm^{-1} : 2737, 2631, 2544, 1653, 1624, 1507, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.96 (9H, s), 1.30-2.05 (7H, m), 2.29 (3H, s), 2.25-2.35 (2H, m), 2.35-3.35 (4H, m), 2.87 (2H, t, J=6 Hz), 4.12 (2H, t, J=6 Hz), 4.25-5.20 (3H, m), 5.80-7.40 (11H, m)

Exemple 68

7-(2-(2-cyclopentylidèneéthyl)-5-méthyl-oxazol-4-yl)éthyl)-2-(2,4-bis(méthyl)-1,2,3,4-tétrahydroquinolin-3(2H)-carboxyle de ter-butylamine

IR v (KBr) cm^{-1} : 2739, 2631, 2542, 1633, 1624, 1549, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.01 (9H, s), 1.40-2.00 (8H, m), 2.10-2.40 (2H, m), 2.27 (3H, s), 2.45-3.40 (6H, m), 2.86 (2H, t, J=6 Hz), 4.12 (2H, t, J=6 Hz), 4.25-5.20 (3H, m), 5.80-7.40 (11H, m), 8.93 (1H, s)

Exemple 69

2-cyclopentylidèneéthyl-7-(2-(5-méthyl-2-(4-méthyl-trans-1-penten-1-yl)oxazol-4-yl)éthyl)-1,2,3,4-tétrahydroquinolin-3(2H)-carboxyle de ter-butylamine

IR v (KBr) cm^{-1} : 2745, 2636, 2554, 1653, 1536, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.94 (9H, s), 0.97 (9H, s), 1.43-2.00 (5H, m), 2.11 (2H, t, J=6 Hz), 2.28 (3H, s), 2.30-2.8 (4H, m), 2.86 (2H, t, J=6 Hz), 2.90-3.40

(2H, m), 4.11 (2H, t, J=6.8Hz), 4.20-4.28 (3H, m), 5.93-6.28 (1H, m), 6.40-6.80 (3H, m), 6.80-7.20 (4H, m)

Exemplo 70

2-metiletilideneacetil-7-(2-(3-metil-2-(4-metil-trans-1-penten-1-il)acetil-4-il)etnil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de ter-butilamina

IR v (NaCl) cm^{-1} : 2743, 2837, 2884, 2916, 1639, 1594, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.93 (6H, d, J=6.4Hz), 1.02 (9H, s), 1.33-1.80 (7H, m), 2.80-3.50 (4H, m), 2.26 (3H, s), 2.86 (2H, t, J=6.7Hz), 2.95-3.42 (2H, m), 4.11 (2H, t, J=6.7Hz), 4.27-5.20 (3H, m), 5.64 (1H, d, J=7.7Hz), 6.16 (1H, d, J=14.6Hz), 6.40-6.80 (3H, m), 6.80-7.30 (4H, m)

Exemplo 71

7-(2-(2-(5-ter-butilacetil-trans-1-penten-1-il)-5-metilacetil-4-il)etnil)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR v (nato) cm^{-1} : 2928, 2864, 1740, 1638, 1612, 1578, 1533, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.22 (9H, s), 1.60-2.00 (1H, m), 1.98 (1H, br-s), 2.15-2.40 (2H, m), 2.27 (3H, s), 2.36 (2H, t, J=7.2Hz), 2.80-3.05 (2H, m), 2.86 (2H, t, J=6.7Hz), 3.33-3.60 (1H, m), 3.78 (2H, s), 4.04 (2H, br-s), 4.16 (2H, t, J=6.7Hz), 6.17 (1H, d, J=16.8Hz), 6.40-6.80 (3H, m), 6.80 (1H, d, J=6.3Hz)

Exemplo 72

7-(2-(2-(5-ter-butilacetil-trans-1-penten-1-il)-5-metilacetil-4-il)etnil)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR v (nato) cm^{-1} : 2937, 2926, 2862, 1740, 1635, 1612, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.22 (9H, s), 1.60-2.00 (1H, m), 2.18-2.40 (2H, m), 2.28 (3H, s), 2.27 (2H, t, J=7.2Hz), 2.87 (2H, t, J=6.6Hz), 3.00-3.25 (2H, m), 3.50 (3H, s), 4.19 (2H, t, J=6.6Hz), 4.35-5.60 (3H, m), 5.80-6.25 (7H, m), 7.04 (1H, d, J=6.6Hz), 7.15-7.30 (1H, m)

Exemplo 73

7-(2-(2-(5-ter-butilacetil-trans-1-penten-1-il)-5-metilacetil-4-il)etnil)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de ter-butilamina

IR v (NaCl) cm^{-1} : 2743, 2835, 2840, 1742, 1685, 1628, 1601, 1555, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.00 (9H, s), 1.32 (9H, s), 1.60-2.00 (3H, m), 2.15-2.40 (2H, m), 2.28 (3H, s), 2.56 (2H, t, J=7.2Hz), 2.86 (2H, t, J=6.3Hz), 2.90-3.25 (2H, m), 4.11 (2H, t, J=6.3Hz), 4.20-5.19 (3H, m), 5.80-7.35 (12H, m)

Exemplo 74

7-(2-(2-(5-dimetilacetil-trans-1-penten-1-il)-5-metilacetil-4-il)etnil)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de metila

IR v (nato) cm^{-1} : 3484, 2948, 2860, 2810, 2770, 1743, 1655, 1626, 1603, 1533, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.40-1.95 (3H, m), 2.10-2.40 (4H, m), 2.23 (6H, s), 2.28 (3H, s), 2.57 (2H, t, J=6.6Hz), 3.03-3.25 (2H, m), 3.59 (3H, m), 4.14 (2H, t, J=6.6Hz), 4.60-5.00 (2H, m), 5.40-5.70 (1H, m), 6.00-6.60 (7H, m), 6.80-7.35 (2H, m)

Exemplo 75

7-(2-(2-(5-dimetilacetil-trans-1-penten-1-il)-5-metilacetil-4-il)etnil)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de sodio

IR v (NaCl) cm^{-1} : 3381, 2786, 2725, 1651, 1595, 1535, 1504

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.40-1.95 (3H, m), 2.05-2.60 (4H, m), 2.25 (6H, s), 2.65-3.10 (4H, m), 3.90-4.10 (2H, m), 4.40-4.80 (2H, m), 5.05-5.25 (1H, m), 5.60-6.75 (7H, m), 6.60-7.25 (2H, m)

Exemplo 76

7-(2-(2-(5-metil-2-(4-metil-trans-1-penten-1-il)acetil-4-il)etnil)-1,2,3,4-tetrahidroquinolina-(3H)-carbonilato de ter-butilamina

IR v (NaCl) cm^{-1} : 1661, 1616, 1558, 1508

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.75-2.20 (3H, m), 0.93 (6H, d, J=6.4Hz), 1.02 (9H, s), 1.20-1.60 (2H, m), 1.60-1.95 (1H, m), 1.95-2.30 (4H, m), 2.10 (2H, t, J=6.6Hz), 2.27 (3H, s),

2 86(2H, t, J=6 Hz), 3 00-3 40(2H, m), 4 10(2H, t, J=6 Hz), 4 40-5 20(2H, m), 6 15(1H, d, J=16 Hz), 6 10-7 20(2H, m).

Exemplu 77

2-(2,4-benzodioxil)-7-(2-[2-(4-metil-trans-3-penten-1-il)oxazol-4-il]stiril)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

IR v (Nujol) cm^{-1} : 3438, 2729, 2632, 2848, 2814, 1657, 1630, 1551, 1504.

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0 84(2H, d, J=6 Hz), 0 97(2H, s), 1 00-1 00(4H, m), 2 13(2H, t, J=6 Hz), 2 00-3 20(2H, m), 3 03(2H, t, J=6 Hz), 4 15(2H, t, J=6 Hz), 4 20-5 20(2H, m), 6 00-7 30(12H, m), 7 30(1H, s)

Exemplu 78

7-(2-[2-(trans-2-ciclohexilvinil)oxazol-4-il]stiril)-2-(2,4-benzodioxil)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0 99(2H, s), 1 20-2 05(12H, m), 2 30-2 72(12H, m), 2 90-3 40(2H, m), 2 94(2H, t, J=6 Hz),

Exemplu 81

2-(2-benzodioxil)-7-(2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]stiril)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

IR v (Nujol) cm^{-1} : 3435, 2729, 2632, 2848, 2814, 1661, 1622, 1543, 1504

$^1\text{H-NMR}(\text{CH}_2\text{Cl}_2-\text{d}_2)$ δ (ppm): 0 80-1 00(3H, m), 0 90(2H, d, J=6 Hz), 1 14(2H, s), 1 20-1 90(2H, m), 1 95-2 25(2H, m), 2 70-3 40(3H, m), 4 10-5 20(2H, m), 6 10-6 05(2H, m), 7 00(1H, d, J=6 Hz), 7 70(1H, s)

Exemplu 82

2-(2,4-benzodioxil)-7-(2-[2-(trans-1-buten-1-il)oxazol-4-il]stiril)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0 72-1 16(3H, m), 0 96(2H, s), 1 20-1 00(4H, m), 1 70-2 00(3H, m), 2 07-2 40(2H, m), 2 00-3 30(2H, m), 2 95(2H, t, J=6 Hz), 4 16(2H, t, J=6 Hz), 4 25-5 20(3H, m), 5 90-7 40(12H, m), 7 49(1H, s)

4 14(2H, t, J=6 Hz), 4 20-5 20(3H, m), 5 00-7 30(12H, m), 7 80(1H, s)

Exemplu 79

7-(2-[2-(trans-2-ciclohexilvinil)oxazol-4-il]stiril)-2-(2,4-benzodioxil)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0 84(2H, s), 1 00-2 40(14H, m), 2 90-3 30(2H, m), 2 94(2H, t, J=6 Hz), 4 14(2H, t, J=6 Hz), 4 20-5 20(2H, m), 5 00-7 47(12H, m), 7 49(1H, s)

Exemplu 80

2-(2-heptadecil)-7-(2-[2-(4-metil-trans-1-penten-1-il)oxazol-4-il]stiril)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0 75-2 20(2H, m), 0 83(2H, d, J=6 Hz), 1 02(2H, s), 1 20-3 60(4H, m), 1 60-1 95(12H, m), 1 95-2 30(2H, m), 2 10(2H, t, J=6 Hz), 2 95(2H, t, J=6 Hz), 3 00-3 40(2H, m), 4 15(2H, t, J=6 Hz), 4 40-5 20(3H, m), 6 15(1H, d, J=16 Hz), 6 10-7 30(2H, m), 7 40(1H, s)

Exemplu 83

2-(2,4-benzodioxil)-7-(2-[2-(1-metil-trans-1-penten-1-il)oxazol-4-il]stiril)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0 80-1 00(2H, m), 0 97(2H, s), 1 11-1 70(2H, m), 1 70-1 93(3H, m), 1 93-2 35(2H, m), 2 01(2H, s), 2 90-3 40(2H, m), 2 96(2H, t, J=6 Hz), 4 14(2H, t, J=6 Hz), 4 24-5 20(3H, m), 5 02-7 30(12H, m), 7 80(1H, s)

Exemplu 84

2-(2,4-benzodioxil)-7-(2-[2-(1-metil-trans-1-buten-1-il)oxazol-4-il]stiril)-1,2,3,4-tetrahidroisocuinolin-(3H)-carboxilato de ter-butilamina

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0 99(2H, s), 1 05(2H, t, J=7 Hz), 1 05-1 95(3H, m), 2 01(2H, s), 2 05-2 45(2H, m), 2 90-3 30(2H, m), 2 96(2H, t, J=6 Hz), 4 15(2H, t, J=6 Hz), 4 25-5 20(3H, m), 5 90-7 30(12H, m)

Exemplu 85

3-(2,4-benzodioxol-1-yl)-7-((2-metil-trans-1-hexen-1-il)oxocel-4-il)etoxi-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de ter-butilamina

¹H-NMR(CCl₄) δ (ppm): 0.90(3H, d, J=6 Hz), 0.97(9H, s), 1.20-1.70(2H, m), 1.70-1.80(3H, m), 2.00-2.40(2H, m), 2.90-3.25(2H, m), 2.95(2H, t, J=6 Hz), 4.15(2H, t, J=6 Hz), 4.35-5.20(2H, m), 5.75-7.30(12H, m), 7.80(1H, s)

Ejemplo de referencia 1

3-(ter-butoxicarbonil)-7-hidroxi-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de etilo

(1) Se suspendió dihidrato de 3,8-dioxo-1-tirnezina (25 g) en ácido clorhídrico concentrado (250 ml), y se agregaron sucesivamente 1,2-dimetoxietano (10 ml) y formalina al 37 % (20 ml). La mezcla se calentó a 70° C durante 30 minutos. A la mezcla de reacción se agregaron ácido clorhídrico concentrado (120 ml), 1,2-dimetoxietano (9 ml) y formalina al 37 % (10 ml), y la mezcla se agitó a 70° C durante 10 horas. Los cristales precipitados se recogieron por filtración y se lavaron con 1,2-dimetoxietano (20 ml) para obtener clorhidrato de ácido 7-

estabilicas a temperatura ambiente y 3,0 kgf/cm² durante 3 horas. El Pd-C se filtró y el metanol se evaporó a presión reducida. Se agregó acetato de etilo (100 ml) al residuo obtenido, y la mezcla se lavó con salmuera saturada (100 ml) y se sacó (Na₂SO₄). El acetato de etilo se evaporó a presión reducida para obtener 7-hidroxi-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de etilo (1,14 g)

IR ν (KBr) cm⁻¹: 1732, 1607, 1510

¹H-NMR(CCl₄) δ (ppm): 1.20 (3H, t, J=7 Hz), 2.00-3.10 (2H, m), 3.00-3.80 (1H, m), 3.97 (2H, s), 4.03-4.20 (4H, m), 4.43 (1H, s), 6.80-6.80 (1H, m), 6.82 (1H, d, J=6 Hz)

(4) El compuesto (1,13 g) obtenido en el punto anterior (3) se disolvió en tetrahidrofurano (20 ml) y se agregó di-ter-butildicarbonato (1,5 g). La mezcla se agitó a temperatura ambiente durante 1 hora y se adicionó acetato de etilo (30 ml). La mezcla se lavó con salmuera saturada (20 ml) y se sacó (Na₂SO₄). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (1,51 g)

IR ν (KBr) cm⁻¹: 3260, 1735, 1671, 1615, 1506

hidroxi-6,8-dioxo-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilico (12,8 g)

IR ν (KBr) cm⁻¹: 1751, 1509, 1570

¹H-NMR(CCl₄) δ (ppm): 3.00-3.30 (2H, m), 4.05 (2H, s), 4.30 (1H, dd, J=5 Hz, 8 Hz), 7.71 (1H, s)

(2) El compuesto (12,8 g) obtenido en el punto anterior (1) se suspendió en etanol (500 ml) y se agregó ácido clorhídrico concentrado (10 ml). La mezcla se mantuvo a reflujo durante 10 horas. El etanol se evaporó a presión reducida, y se agregó acetato de etilo (300 ml). La mezcla se lavó con hidrogenocarbonato de sodio saturado acuoso (100 ml) y salmuera saturada (100 ml), y se sacó (Na₂SO₄). El acetato de etilo se evaporó a presión reducida para obtener 7-hidroxi-6,8-dioxo-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de etilo (11,11 g)

¹H-NMR(CCl₄) δ (ppm): 1.20 (3H, t, J=7 Hz), 2.00-3.00 (2H, m), 3.30-4.10 (2H, m), 4.33 (2H, s, J=7 Hz), 7.40 (1H, s)

(3) Se suspendió Pd-C al 10 % (350 mg) en metanol (60 ml), y se agregaron el compuesto (2,8 g) de (2) y trietilamina (2,0 ml). La mezcla se sometió a hidrogenación

¹H-NMR(CCl₄) δ (ppm): 1.20 (3H, t, J=7 Hz), 1.47 (3H, s), 2.00 (2H, d, J=5 Hz), 4.2 (2H, q, J=7 Hz), 4.41 (1H, s, J=15 Hz), 4.80-5.25 (1H, m), 4.53 (1H, d, J=15 Hz), 5.00-5.00 (1H, br), 6.30-6.30 (2H, m), 6.30 (1H, d, J=6 Hz)

Ejemplo de referencia 2

3-(ter-butoxicarbonil)-7-hidroxi-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de metilo

El compuesto que figura en el título se obtuvo de la misma manera que en el ejemplo de referencia 1

IR ν (KBr) cm⁻¹: 3261, 1755, 1672, 1614, 1506

¹H-NMR(CCl₄) δ (ppm): 1.47 (3H, s), 2.00 (2H, d, J=5 Hz), 3.63 (2H, s), 4.40 (1H, d, J=16 Hz), 4.60-5.25 (1H, m), 4.66 (1H, d, J=16 Hz), 5.00-5.00 (1H, br), 6.30-6.30 (2H, m), 6.30 (1H, d, J=6 Hz)

Ejemplo de referencia 3

3-(2,4-benzodioxol-1-yl)-7-hidroxi-1,2,3,4-tetrahidroisoquinolin-(3H)-carbonilato de metilo

Se disolvió 7-hidroxi-1,2,3,4-tetrahidroisquinolina-(3H)-carbonilato de metilo (1,24 g) en cloruro de metileno (25 ml) y se agregó trietilamina (5,5 ml), seguida por adición por gotas de cloruro de ácido acético (3,1 ml) bajo enfriamiento con hielo. Esto se agitó a la misma temperatura durante 15 minutos, se lavó con solución acuosa de ácido cítrico al 10 % (20 ml), hidrogenocarbonato de sodio saturado acuoso (20 ml) y salmuera saturada (20 ml), y se secó (Na_2SO_4). Se evaporó el cloruro de metileno a presión reducida y el residuo obtenido se purificó por cromatografía en columna. El aceite obtenido (1,04 g) se disolvió en metanol (20 ml), y solución acuosa de hidróxido de litio 1 M (3,0 ml) se agregó de a porciones a temperatura ambiente. Tras acidificar con solución acuosa de ácido cítrico al 10 %, la mezcla se extrajo con acetato de etilo (50 ml). La capa de acetato de etilo se lavó con salmuera saturada (20 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (0,83 g).

IR v (nato) cm^{-1} : 3184, 1734, 1576, 1506

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.64 (3H, d, J=5.9 Hz), 2.00-2.40 (2H, m), 2.86 (3H, s), 4.20-5.10 (2H, m), 5.30-5.60

(1H, m), 5.70-6.50 (4H, m), 6.64 (1H, s), 6.66 (1H, d, J=7.9 Hz), 6.99 (1H, d, J=7.9 Hz), 7.15-7.50 (1H, m)

Ejemplo de referencia 4

2-(2-hidroxi-1,2,3,4-tetrahidroisquinolina-3H)-carbonilato de metilo

Se disolvió 7-hidroxi-1,2,3,4-tetrahidroisquinolina-(3H)-carbonilato de metilo (0.8 g) en cloruro de metileno (10 ml), y se agregaron ácido 8-heptanoico (1.35 g) y clorhidrato de 1-etil-3-(3'-dimetilaminopropil)carbodiimida (2.00 g). La mezcla se agitó a temperatura ambiente durante 30 minutos. Se agregó cloruro de metileno (20 ml), y la mezcla se lavó con solución acuosa de ácido cítrico al 10 % (20 ml) y salmuera saturada (20 ml), y se secó (Na_2SO_4). Se evaporó el cloruro de metileno a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (1.15 g).

IR v (nato) cm^{-1} : 3375, 1740, 1555, 1503, 1500

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.90 (3H, br-t), 1.10-1.70 (4H, m), 1.80-2.40 (2H, m), 3.00-3.40 (2H, m), 3.89 (2H, s), 4.35-5.15 (4H, m), 6.36 (1H, d, J=15.2 Hz), 6.25-6.80 (1H, m), 6.64 (1H, s), 6.80-7.20 (1H, m), 6.99 (1H, d, J=7.9 Hz)

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Ejemplo de referencia 5

2-(2-etil-3-oxo-1,2,3,4-tetrahidroisquinolina-4-il)acetato

(1) Se suspendió β -etil-L-aspartato (20 g) en cloruro de metileno (400 ml), y se agregó cloruro de cloruro de cloruro (10.14 g). Se agregó por gotas trietilamina (53 ml) a -5°C y la mezcla se agitó a la misma temperatura durante 1,5 horas. La mezcla de reacción se extrajo cinco veces con agua (300 ml), y la capa acuosa se acidificó con ácido clorhídrico 5 M y se extrajo con acetato de etilo (500 ml). La capa de acetato de etilo se lavó con salmuera saturada (300 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido (13,3 g) se disolvió en tolueno (100 ml). Se agregaron anhídrido acético (22,6 ml), N-etilmorfolina (21,1 ml) y 4-dimetilaminopiridina y la mezcla se agitó a 65°C durante 5 horas. Se agregó hidrogenocarbonato de sodio saturado acuoso a la mezcla de reacción, se neutralizó y se separaron las dos capas. La capa de tolueno se lavó con salmuera saturada (100 ml) y se secó (Na_2SO_4). El tolueno se evaporó a presión reducida, y el residuo obtenido (9,1 g) se disolvió en tolueno (50 ml). Se agregó oxicloruro de fosforo (9,2 ml) y la mezcla se calentó a reflujo durante 6 horas. La mezcla de reacción se vertió en agua helada, se

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neutralizó con carbonato de potasio y se separaron las dos capas. La capa de tolueno se lavó con salmuera saturada (100 ml) y se secó (Na_2SO_4). El tolueno se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 2-(2-etil-3-oxo-1,2,3,4-tetrahidroisquinolina-4-il)acetato de metilo (1,31 g).

IR v (nato) cm^{-1} : 1742, 1641

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 2.33 (3H, s), 3.82 (2H, s), 3.73 (2H, s), 6.85 (1H, d, J=16.2 Hz), 7.15-7.50 (4H, m)

(2) El compuesto (1,31 g) obtenido en el punto anterior (1) se disolvió en éter dietílico (25 ml), y se agregó hidruro aluminico de litio (0,23 g) de a porciones a 0°C . La mezcla se agitó a la misma temperatura durante 20 minutos. Se agregó agua (5 ml), se filtró un material insoluble y se separaron las dos capas. La capa de éter dietílico se lavó con salmuera saturada (15 ml) y se secó (Na_2SO_4). El éter dietílico se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (0,55 g).

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 2.31 (3H, s), 2.61 (2H, d, J=6 Hz), 3.20-3.30 (1H, br), 3.64 (2H, d, J=6 Hz), 4.84 (1H, d, J=16 Hz), 7.20-7.30 (6H, m).

Ejemplo de referencia 8

2-(5-metil-2-oxirilanona)-4-ilacetato de metilo

Se disolvió cinnamida (0.9 g) y 4-bromo-3-oxopentanoato de metilo (0.71 g) en N,N-dimetilformamida (2.5 ml) y la mezcla se agitó a 100°C durante 15 horas. Se agregó acetato de etilo (50 ml), y la mezcla se lavó con agua (100 ml) y luego con salmuera saturada (100 ml), y se secó (MgSO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (0.1 g). IR y $^1\text{H-NMR}$ eran iguales que en el ejemplo de referencia 3(1).

Los siguientes compuestos se sintetizaron de la misma manera que en los ejemplos de referencia 8 y 9.

Ejemplo de referencia 7

2-(3-metil-2-(trans-1-penten-1-il)onano)-4-ilacetato

Ejemplo de referencia 10

2-(2-ciclohexil-3-metilonano)-4-ilacetato

IR v (nato) cm^{-1} : 2960, 1742, 1570, 1450

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.10-2.40 (11H, m), 2.21 (3H, s), 2.60-2.80 (1H, m), 2.61 (2H, t, J=5 Hz), 3.65 (1H, br-s), 3.84 (2H, t, J=5 Hz).

Ejemplo de referencia 11

2-(5-metil-2-(trans-1-penten-1-il)onano)-4-ilacetilmetansulfonato

Se disolvió 2-(5-metil-2-(1-penten-1-il)onano)-4-ilacetato (1.63 g) en cloruro de metileno (10 ml), y se agregó trietilamina (1.63 ml). Se adicionó por gotas cloruro de metansulfónico (0.41 ml) a 0°C , y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se agregó acetato de etilo (100 ml), y la mezcla se lavó con solución acuosa de ácido cítrico al 10 % (100 ml) y luego con salmuera saturada (100 ml), y se secó (MgSO_4). El solvente se evaporó a presión reducida para obtener el compuesto que figura en el título (1.1 g).

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IR v (nato) cm^{-1} : 2960, 1664, 1634, 1611, 1534

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.95 (3H, t, J=7 Hz), 1.20-1.80 (2H, m), 2.00-2.40 (2H, m), 2.25 (3H, s), 2.64 (2H, t, J=6 Hz), 2.70-3.20 (1H, br), 3.66 (2H, t, J=5 Hz), 6.17 (1H, d, J=6 Hz), 6.64 (1H, dt, J=6, 8 Hz).

Ejemplo de referencia 9

2-(2-metil-2-oxirilanona)-4-ilacetato

IR v (nato) cm^{-1} : 2941, 1570

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.90 (3H, br-t), 1.20-1.50 (4H, m), 1.80-1.95 (2H, m), 2.21 (3H, s), 2.45-2.80 (4H, m), 3.00 (1H, br-s), 3.55 (2H, t, J=5 Hz).

Ejemplo de referencia 2

2-(2-ciclohexil-3-metilonano)-4-ilacetato

IR v (nato) cm^{-1} : 2941, 1572

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 1.40-2.30 (6H, m), 2.21 (3H, s), 2.61 (2H, t, J=6 Hz), 2.95-3.30 (1H, m), 3.36 (1H, br-s), 3.84 (2H, t, J=6 Hz).

IR v (nato) cm^{-1} : 1694, 1643, 1531, 1534

$^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 0.90 (3H, t, J=7 Hz), 1.20-1.80 (2H, m), 2.00-2.40 (2H, m), 2.27 (3H, s), 2.66 (2H, t, J=6 Hz), 2.94 (3H, s), 4.45 (2H, t, J=6 Hz), 6.16 (1H, d, J=16 Hz), 6.60 (1H, dt, J=16, 8 Hz).

Ejemplo de referencia 12

2-(5-epil-2-oxiriltiano)-4-ilacetilmetansulfonato

(1) Se disolvió cinnamida (3.27 g) en tetrahidrofurano (13 ml), y se agregó reactivo de Lunnson (4.94 g). La mezcla se mantuvo a reflujo durante 3 horas y se agregó 4-bromo-3-oxopentanoato de metilo (6.97 g). La mezcla se mantuvo a reflujo durante otras 11 horas. El tetrahidrofurano se evaporó a presión reducida y se agregó acetato de etilo (300 ml) al residuo obtenido. La mezcla se lavó con agua (200 ml) y luego con salmuera saturada (200 ml), y se secó (MgSO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 2-(5-metil-2-oxiriltiano)-4-ilacetato de metilo (2.8 g).

IR v (Nujol) cm^{-1} : 1732, 1695, 1573, 1537

¹H-NMR(CDCl₃) δ(ppm): 2.41 (3H, s), 3.72 (3H, s), 3.75 (2H, s), 7.15-7.60 (7H, m)

(2) El compuesto (2.85 g) obtenido en el punto anterior (1) se disolvió en tolueno (10.7 ml), y se agregó por gotas una solución de hidrato de diisobutilaluminio-tolueno 1.5 N (10.7 ml) a -10° C. La mezcla se agitó a la misma temperatura durante 1 hora y se agregó (3 ml) Se filtró un material indisoluble y se separaron las dos capas. La capa de tolueno se lavó con salmuera saturada (10 ml) y se secó (Na₂SO₄). El tolueno se evaporó a presión reducida y el 2-(5-metil-2-oxociclohexil-4-il)etanol crudo obtenido (2.8 g) se disolvió en alcohol de metileno (30 ml). Se adicionó trietilamina (1.05 ml), y se agregó por gotas cloruro de metansulfónico (0.97 ml) a 0° C. La mezcla se agitó a temperatura ambiente durante 20 minutos. Se agregó acetato de etilo (200 ml), y la mezcla se lavó con solución acuosa de ácido cítrico al 10 % (200 ml) y luego con salmuera saturada (100 ml), y se secó (Na₂SO₄). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (1.1 g)

¹H-NMR(CDCl₃) δ(ppm): 2.42 (3H, s), 2.91 (3H, s), 3.11 (2H, t, J=6 Hz), 4.87 (2H, t, J=6 Hz), 7.00-7.63 (7H, m)

(Na₂SO₄). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (1.00 g)

IR ν (neq) cm⁻¹: 2700-3100, 1445, 1360, 1315, 1043, 762, 694, 539

¹H-NMR(CDCl₃) δ(ppm): 2.27 (2H, s), 3.0-4.1 (2H, m), 4.2-4.5 (2H, m), 7.2-7.5 (3H, m), 7.5-7.8 (2H, m)

Los siguientes compuestos se sintetizaron de la misma manera que en el ejemplo de referencia 11

Ejemplo de referencia 14

2-((1-feniletildien)amino)etilmetansulfonato

IR ν (NaJol) cm⁻¹: 1254, 1177, 1069, 1018, 924, 864, 764, 696, 539

¹H-NMR(CDCl₃) δ(ppm): 2.26 (2H, s), 3.62 (2H, s), 4.3-4.7 (4H, m), 7.2-7.5 (3H, m), 7.5-7.8 (2H, m)

Ejemplo de referencia 15

Ejemplo de referencia 12

2-((1-feniletildien)amino)etanol

Se disolvió acetofenoniina (1.00 g) y 2-(2-bromotol)tetrahidropirano (3.00 g) en N,N-dimetilacetamida (30 ml), y se agregó carbonato de potasio (7.10 g). La mezcla se agitó a 80° C durante 10 horas. Luego de dejar enfriar, se agregó agua (100 ml) a la mezcla de reacción. La mezcla se extrajo dos veces con acetato de etilo (50 ml). Las capas de acetato de etilo se combinaron, se lavaron con agua (50 ml) y luego con salmuera saturada (50 ml), y se secaron (Na₂SO₄). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener un aceite incoloro (2.01 g). El aceite obtenido (1.99 g) se disolvió en metanol (30 ml), y se agregó monohidrato de p-ácido toluensulfónico (1.73 g). La mezcla se agitó a temperatura ambiente durante 1 hora. El metanol se evaporó a presión reducida y se adicionó solución saturada acuosa de hidrogenocarbonato de sodio (30 ml). La mezcla se extrajo dos veces con acetato de etilo (30 ml). Las capas de acetato de etilo se combinaron y se lavaron con una solución saturada acuosa de hidrogenocarbonato de sodio (30 ml) y luego con salmuera saturada (50 ml), y se secaron

2-(4-metil-2-fenilsulfonilfenil)-3-iletimetansulfonato

(1) Se disolvió tiofenol (1.90 ml) en N,N-dimetilformamida (10 ml). Se agregó de a porciones hidruro de sodio (suspensión en aceite al 60 %, 740 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 15 minutos. A continuación de ello, se agregó por gotas una solución de 2-cloro-4-metilfenil-3-carbonilato de etilo (3.05 g) en N,N-dimetilformamida (10 ml), y la mezcla se agitó a la misma temperatura durante 20 minutos. Se agregó agua (30 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (50 ml). La capa de acetato de etilo se lavó dos veces con agua (50 ml) y luego con salmuera saturada (30 ml), y se secó (Na₂SO₄). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 4-metil-2-fenilsulfonilfenil-3-carbonilato de etilo (3.05 g)

IR ν (neq) cm⁻¹: 1713, 1631

¹H-NMR(CDCl₃) δ(ppm): 1.28 (3H, t, J=7 Hz), 2.47 (3H, s), 4.24 (2H, t, J=7 Hz), 7.40-7.80 (5H, m)

(2) El compuesto (3.05 g) obtenido en el punto anterior (1) se disolvió en tetrahidrofureno (80 ml), y se

agregó de a porciones hidruro aluminico de litio (436 mg) bajo enfriamiento con hielo. La mezcla se agitó a la misma temperatura durante 15 minutos. Se agregaron agua (20 ml) y acetato de etilo (30 ml), y se filtró un material insoluble. Se separaron las dos capas y la capa de acetato de etilo se lavó con salmuera saturada (20 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 4-metil-2-fenilsulfonilfeniltiosol-5-metanol (3,23 g).

IR v (cinta) cm^{-1} : 3265, 1542, 1555

$^1\text{H-NMR}(\text{CDCl}_3)$ $\delta(\text{ppm})$: 2.31 (3H, s), 2.50 (1H, s), 4.65 (2H, s), 7.30-7.70 (5H, m)

(3) El compuesto (7,30 g) obtenido en el punto anterior (2) se disolvió en cloruro de metileno (100 ml). Se agregó trietilamina (6,40 ml) y se adicionó por gotas cloruro de metansulfonilo (1.96 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se lavó con agua fría (20 ml) y se secó (Na_2SO_4). Se evaporó el cloruro de metileno a presión reducida y el residuo obtenido se disolvió en acetonitrilo (100 ml). Se agregó cianuro de sodio (2,26 g) y 10-corona-6 (1,30 g), y la mezcla se agitó a 60°C

IR v (cinta) cm^{-1} : 1740

$^1\text{H-NMR}(\text{CDCl}_3)$ $\delta(\text{ppm})$: 2.33 (3H, s), 3.64 (2H, s), 3.89 (3H, s), 6.30-6.70 (5H, m)

(5) El compuesto (2,77 g) obtenido en el punto anterior (4) se disolvió en tetrahidrofurano (53 ml), y se agregó hidruro aluminico de litio (376 mg) de a porciones bajo enfriamiento con hielo. La mezcla se agitó a la misma temperatura durante 15 minutos. Se adicionaron agua (20 ml) y acetato de etilo (30 ml), y se filtró un material insoluble. Se separaron las dos capas y la capa de acetato de etilo se lavó con salmuera saturada (20 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 2-(4-metil-2-fenilsulfonilfeniltiosol-5-il)etanol (2,49 g).

IR v (cinta) cm^{-1} : 3302

$^1\text{H-NMR}(\text{CDCl}_3)$ $\delta(\text{ppm})$: 1.60-2.00 (1H, br), 2.33 (3H, s), 2.89 (2H, t, J=6 Hz), 3.75 (2H, t, J=6 Hz), 7.30-7.70 (5H, m)

durante 2 horas. El acetonitrilo se evaporó a presión reducida y se agregó acetato de etilo (100 ml) al residuo obtenido. La mezcla se lavó dos veces con agua (20 ml) y luego con salmuera saturada (30 ml) y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener 4-metil-2-fenilsulfonilfeniltiosol-5-il)acetato de etilo (2,00 g).

IR v (cinta) cm^{-1} : 2254, 1502, 1555

$^1\text{H-NMR}(\text{CDCl}_3)$ $\delta(\text{ppm})$: 2.34 (3H, s), 3.66 (2H, s), 7.40-7.70 (5H, m)

(4) El compuesto (2,00 g) obtenido en el punto anterior (3) se disolvió en ácido clorhídrico concentrado (5.6 ml) y la mezcla se agitó a 100°C durante 20 minutos. Se agregó metanol (120 ml) a la mezcla de reacción y la mezcla se mantuvo a reflujo durante 1 hora. El metanol se evaporó a presión reducida y se agregó acetato de etilo (30 ml) al residuo obtenido. La mezcla se lavó con agua (20 ml), hidrogenocarbonato de sodio saturado acuoso (20 ml) y luego con salmuera saturada (30 ml), y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida para obtener 4-metil-2-fenilsulfonilfeniltiosol-5-il)acetato de metilo (2,77 g).

(6) El compuesto (2,49 g) obtenido en el punto (5) anterior se disolvió en cloruro de metileno (25 ml), y se agregó trietilamina (2,0 ml). El cloruro de metansulfonilo (0.93 ml) se agregó por gotas y luego se enfrió con hielo, la mezcla se agitó a la misma temperatura durante 30 minutos. La mezcla se lavó con solución acuosa de ácido cítrico al 10 % (20 ml), hidrogenocarbonato de sodio saturado acuoso (20 ml) y luego con salmuera saturada (20 ml), y se secó (Na_2SO_4). Se evaporó el cloruro de metileno a presión reducida, y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (1,81 g).

IR v (cinta) cm^{-1} : 1502, 1551

$^1\text{H-NMR}(\text{CDCl}_3)$ $\delta(\text{ppm})$: 2.34 (3H, s), 3.92 (2H, s), 3.89 (2H, t, J=6 Hz), 4.36 (2H, t, J=6 Hz), 7.30-7.70 (5H, m)

Ejemplo de referencia 16

2-(5-metil-2-(4-metil-trans-2-hexanamida-1-il)metanol-4-il)acetato de metilo

Se suspendió 5-metil-trans-2-hexanamida (5,7 g) en tolueno (30 ml) y se agregó 4-bromopropionilacetato de metilo (14,0 g). La mezcla se mantuvo a reflujo durante 14

horas. Se agregó acetato de etilo (50 ml), y la mezcla se lavó sucesivamente con agua (50 ml) y salmuera saturada (50 ml), y se secó (Na_2SO_4). El solvente se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (3.38 g).

IR v (nato) cm^{-1} : 2957, 2926, 2870, 1740, 1643, 1551

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.94 (6H, d, J=6 Hz), 1.50-2.10 (1H, m), 2.11 (2H, t, J=6 Hz), 2.27 (3H, s), 3.40 (2H, s), 3.71 (2H, s), 6.17 (1H, d, J=16 Hz), 6.61 (1H, dt, J=6 Hz, 16 Hz).

Ejemplo de referencia 17

3-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)acetato de metilo

(1) Se disolvió β -metil-L-aspartato (44.00 g) en agua (320 ml), y se agregó carbonato de sodio (97.50 g). Se agregó tetrahidrofurano (110 ml) y se adicionó por gotas cloruro de 3-metil-trans-2-hexenoilo (42.1 g). La mezcla se agitó a temperatura ambiente durante 15 horas y se agregó agua (320 ml). La mezcla se lavó con acetato de etilo (110 ml), y la capa acuosa se ajustó a un valor de pH de 2 con

(2) El compuesto (6.4 g) obtenido en el punto anterior (1) se disolvió en tolueno (5.4 ml), y se agregó cloruro de fosforo (6.30 ml). La mezcla se mantuvo a reflujo durante 1 hora. La mezcla de reacción se vertió en agua helada (10 ml), y tras neutralizar con bicarbonato de sodio, se separaron las dos capas. La capa de tolueno se lavó con salmuera saturada (10 ml) y se secó (Na_2SO_4). El tolueno se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (0.9 g).

IR y $^1\text{H-NMR}$ eran iguales a los del ejemplo de referencia 16.

Ejemplo de referencia 18

3-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)acetato

El compuesto (3.34 g) del ejemplo de referencia 15 se disolvió en tolueno (30 ml) y se agregó por gotas una solución de hidruro de diisobutilaluminio-tolueno 1.5 N (37.5 ml) a -70°C . La mezcla se agitó de -70°C a -40°C durante 1 hora. La mezcla de reacción se vertió en agua (100 ml) y se filtró un material insoluble, después de lo

ácido clorhídrico concentrado y se extrajo con acetato de etilo (400 ml). La capa de acetato de etilo se lavó sucesivamente con agua y salmuera saturada (150 ml cada una), y se secó (Na_2SO_4). El acetato de etilo se evaporó a presión reducida para obtener un aceite (39.7 g). El aceite obtenido se disolvió en tolueno (220 ml), y se agregaron anhídrido acético (60 ml), piridina (32 ml) y 4-dimetilaminopiridina (3.2 g). La mezcla se agitó a 65°C durante 5 horas. La mezcla de reacción se lavó con agua (300 ml) y ácido clorhídrico 1 N (300 ml). Se agregó agua (300 ml) a la capa de tolueno y la mezcla se neutralizó con bicarbonato de sodio. Se separaron las dos capas, y la capa de tolueno se lavó con salmuera saturada (200 ml) y se secó (Na_2SO_4). El tolueno se evaporó a presión reducida y se agregó n-hexano al residuo obtenido. Los cristales precipitados se recogieron por filtración para obtener 3-(5-metil-trans-2-hexenoilamino)-4-oxo-pentamato de metilo (27.42 g).

IR v (nato) cm^{-1} : 3329, 1747, 1720, 1664, 1616, 1521

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.93 (6H, d, J=6 Hz), 1.50-2.00 (1H, m), 2.09 (2H, t, J=7 Hz), 2.25 (3H, s), 2.70, 3.06 (2H, ABq, J=4, 17 Hz), 3.69 (2H, s), 4.70-4.95 (1H, m), 5.83 (1H, d, J=15 Hz), 6.45-7.00 (1H, br), 6.80 (1H, dt, J=7 Hz, 15 Hz).

cual se separaron las dos capas. La capa de tolueno se lavó con salmuera saturada (50 ml) y se secó (Na_2SO_4). El tolueno se evaporó a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (1.75 g).

IR v (nato) cm^{-1} : 3346, 2957, 2926, 2870, 1661, 1641, 1533

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.94 (6H, d, J=6 Hz), 1.50-2.10 (1H, m), 2.11 (2H, t, J=7 Hz), 2.25 (3H, s), 2.71 (2H, t, J=5 Hz), 2.91 (1H, br-s), 3.06 (2H, t, J=5 Hz), 6.16 (1H, d, J=15 Hz), 6.62 (1H, dt, J=7, 15 Hz).

Ejemplo de referencia 19

3-(5-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il)acetato de metileno

El compuesto (1.77 g) del ejemplo de referencia 18 se disolvió en cloruro de metileno (50 ml) y se agregó trietilamina (2.3 ml). El cloruro de metanesulfónico (0.77 ml) se agregó por gotas a 0°C y la mezcla se agitó a temperatura ambiente durante 20 minutos. Se adicionó cloruro de metileno (30 ml), se lavó con solución acuosa de ácido cítrico al 10 % (30 ml) y luego con salmuera saturada

(36 ml). y se secó (Na₂SO₄). Se evaporó el disolvente de metileno a presión reducida y el residuo obtenido se purificó por cromatografía en columna para obtener el compuesto que figura en el título (2 21 g)

IR ν (neat) cm⁻¹: 2929, 2920, 2870, 1643 1533

¹H-NMR (CDCl₃) δ (ppm): 0.84 (6H, d, J=6.4 Hz), 1.30-2.10 (1H m), 2.12 (2H, t, J=7.0 Hz), 2.27 (3H, s), 3.87 (2H, t, J=6.7 Hz), 3.94 (3H, s), 4.48 (2H, t, J=6.0 Hz), 6.13 (1H, d, J=1.3 Hz), 6.62 (1H, dt, J=7.0, 1.3 Hz)

Los siguientes compuestos se sintetizaron de la misma manera que en el ejemplo de referencia 19

Ejemplo de referencia 20

2-(2-(trans-2-ciclopentilvinil)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (neat) cm⁻¹: 2926 2853 1730, 1643, 1533

¹H-NMR (CDCl₃) δ (ppm): 0.85-2.50 (11H m), 2.20 (3H, s), 2.86 (2H t, J=6.0 Hz), 2.94 (2H, s), 4.44 (2H, t, J=6.0 Hz), 6.11 (1H, d, J=1.6 Hz), 6.46 (1H, dt, J=6.0, 1.6 Hz)

Ejemplo de referencia 21

2-(5-metil-2-(1-metil-trans-1-buten-1-il)oxazol-4-il)etilmetansulfonato

IR ν (neat) cm⁻¹: 2966, 2934, 2876, 1647, 1572, 1535

¹H-NMR (CDCl₃) δ (ppm): 1.07 (2H t, J=6.0 Hz), 2.00 (3H, s), 2.05-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.0 Hz), 2.94 (3H, s), 4.43 (2H, t, J=6.0 Hz), 6.48 (1H, br-t)

Ejemplo de referencia 24

2-(3-metil-2-(1-metil-trans-1-penten-1-il)oxazol-4-il)etilmetansulfonato

IR ν (neat) cm⁻¹: 2983, 2961, 2932, 2872, 1647, 1535

¹H-NMR (CDCl₃) δ (ppm): 0.96 (3H, t, J=7.0 Hz), 1.20-1.73 (2H, m), 2.00 (3H s), 2.00-2.40 (2H, m), 2.27 (3H, s), 2.87 (2H, t, J=6.0 Hz), 2.94 (3H s), 4.43 (2H t, J=6.0 Hz), 6.48 (1H, dt, J=1.4, 7.0 Hz)

Ejemplo de referencia 25

Ejemplo de referencia 21

2-(2-(trans-1-buten-1-il)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (neat) cm⁻¹: 2929 2420, 2959, 2930, 2880 1730, 1643, 1570, 1533

¹H-NMR (CDCl₃) δ (ppm): 0.75-1.10 (3H, m), 1.10-1.67 (4H, m), 2.04-2.40 (2H, m), 2.27 (3H, s), 2.86 (2H, t, J=6.7 Hz), 2.94 (1H, s), 4.43 (2H t, J=6.7 Hz), 6.16 (1H, d, J=1.6 Hz), 6.64 (1H dt, J=1.6 Hz, 6.2 Hz)

Ejemplo de referencia 22

2-(2-(3-metil-trans-2-buten-1-il)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (neat) cm⁻¹: 2932, 2410, 2857, 2926 2870, 1661, 1643, 1533

¹H-NMR (CDCl₃) δ (ppm): 0.91 (6H, d, J=6.2 Hz), 1.13-1.30 (3H, m), 2.00-2.22 (2H, m), 2.26 (3H, s), 2.86 (2H, t, J=6.7 Hz), 2.94 (3H, s), 4.43 (2H, t, J=6.7 Hz), 6.20 (1H, d, J=1.6 Hz), 6.62 (1H, dt, J=1.3, 7.0 Hz)

2-(2-(trans-2-ciclopentilvinil)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (neat) cm⁻¹: 2955, 2870 1736 1645, 1533

¹H-NMR (CDCl₃) δ (ppm): 1.20-2.00 (5H, m), 2.26 (3H, s), 2.36-2.70 (1H, m), 2.86 (2H, t, J=6.0 Hz), 2.94 (3H, s), 4.44 (2H t, J=6.0 Hz), 6.14 (1H, d, J=1.3 Hz), 6.62 (1H, dt, J=1.3, 7.0 Hz)

Ejemplo de referencia 26

2-(3-metil-2-(2-trans-(1-metilciclopentil)vinil)oxazol-4-il)etilmetansulfonato

IR ν (neat) cm⁻¹: 2926, 2853 1645 1531, 1506

¹H-NMR (CDCl₃) δ (ppm): 1.06 (3H s), 1.20-1.60 (10H m), 2.28 (3H, s), 2.87 (2H, t, J=6.0 Hz), 2.95 (3H, s), 4.43 (2H, t, J=6.0 Hz), 6.12 (1H, d, J=1.6 Hz), 6.63 (1H, d, J=1.6 Hz)

Ejemplo de referencia 27

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2-(5-metil-2-(2-propil-1-metilcyclopentil)vinil)oxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 2957, 2972, 1643, 1591, 1533

¹H-NMR (CDCl₃) δ (ppm): 1.18 (3H, s), 1.40-1.60 (8H, m), 2.27 (3H, s), 2.86 (2H, t, J=6 Hz), 2.94 (3H, s), 4.43 (2H, t, J=6 Hz), 6.13 (1H, d, J=16 Hz), 6.71 (1H, d, J=16 Hz)

Ejemplo de referencia 28

2-(5-metil-4-(2-metil-1-fenil-1-oxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 2923, 1691, 1576

¹H-NMR (CDCl₃) δ (ppm): 2.12 (3H, s), 2.24 (3H, s), 2.60-2.20 (4H, m), 2.85 (2H, t, J=7 Hz), 2.94 (3H, s), 4.43 (2H, t, J=7 Hz)

Ejemplo de referencia 29

2-(2-(3,3-dimetil-trans-1-buten-1-il)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 2962, 2907, 2869, 1660, 1643, 1533

¹H-NMR (CDCl₃) δ (ppm): 1.11 (3H, s), 2.27 (3H, s), 2.86 (2H, t, J=6 Hz), 2.94 (3H, s), 4.43 (2H, t, J=6 Hz), 6.11 (1H, d, J=16 Hz), 6.67 (1H, d, J=16 Hz)

Ejemplo de referencia 30

2-(2-(2,4-dimetil-trans-1-penten-1-il)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 2957, 2907, 2868, 1661, 1643, 1533

¹H-NMR (CDCl₃) δ (ppm): 0.93 (3H, s), 2.10 (2H, d, J=7 Hz), 2.28 (3H, s), 2.87 (2H, t, J=6 Hz), 2.94 (3H, s), 4.43 (2H, t, J=6 Hz), 6.13 (1H, d, J=16 Hz), 6.63 (1H, dt, J=7.5, 1.6 Hz)

Ejemplo de referencia 31

2-(2-(3-etil-trans-1-penten-1-il)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 2943, 2928, 2876, 1643, 1578, 1551, 1533

¹H-NMR (CDCl₃) δ (ppm): 0.86 (3H, t, J=6 Hz), 1.20-1.70 (4H, m), 1.70-2.20 (1H, m), 2.27 (3H, s), 2.87 (2H, t, J=6 Hz), 2.94 (1H, s), 4.43 (2H, t, J=6 Hz), 6.12 (1H, d, J=15 Hz), 6.61 (1H, dd, J=15.8, 7.9 Hz)

Ejemplo de referencia 32

2-(2-(2,3-dimetil-trans-1-penten-1-il)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 3034, 3003, 1643, 1543

¹H-NMR (CDCl₃) δ (ppm): 0.93 (3H, t, J=7 Hz), 1.06 (3H, s), 1.43 (3H, q, J=7 Hz), 2.27 (3H, s), 2.87 (2H, t, J=6.7 Hz), 2.94 (1H, s), 4.43 (2H, t, J=6.7 Hz), 6.09 (1H, d, J=16 Hz), 6.59 (1H, d, J=16 Hz)

Ejemplo de referencia 33

2-(5-metil-2-(1-trans-2-tiofen-2-il)vinil)oxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 3620, 3420, 3107, 3070, 2974, 1734, 1636, 1547

¹H-NMR (CDCl₃) δ (ppm): 2.31 (3H, s), 2.90 (2H, t, J=6 Hz), 2.95 (3H, s), 4.70 (2H, t, J=6 Hz), 6.64 (1H, d, J=16 Hz), 7.02 (1H, dd, J=4.6, 3.2 Hz), 7.16 (1H, d, J=3.2 Hz), 7.29 (1H, d, J=4 Hz), 7.32 (1H, d, J=16 Hz)

Ejemplo de referencia 34

2-(5-metil-2-fenil-1-oxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 2928, 1507

¹H-NMR (CDCl₃) δ (ppm): 2.25 (3H, s), 2.86 (2H, t, J=6 Hz), 2.98 (3H, s), 4.44 (2H, t, J=6 Hz), 7.30-7.15 (5H, m)

Ejemplo de referencia 35

2-(2-(3-metoxi-trans-1-penten-1-il)-5-metiloxazol-4-il)etilmetansulfonato

IR ν (nato) cm⁻¹: 2930, 1354

¹H-NMR (CDCl₃) δ (ppm): 2.29 (3H, s), 2.87 (2H, t, J=6 Hz), 2.94 (3H, s), 3.39 (3H, s), 4.43 (2H, t, J=6 Hz), 5.30-5.08 (2H, m)

Ejemplo de referencia 362-(2-(3-(4-metil-trans-1-penten-1-il)-3-metiloxazol-4-il)etil)metansulfonato

IR ν (neat) cm^{-1} : 2964 2929, 2869 1663, 1643, 1579, 1535

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.69-2.15 (2H, m), 2.20-2.30 (2H, m), 2.27 (3H, s), 2.46 (2H, t, J=6 Hz), 2.94 (3H, s), 4.43 (2H, t, J=6 Hz), 4.49 (2H, dt, J=5.8, 4.7 Hz), 5.21 (1H, d, J=16 Hz), 6.62 (1H, dt, J=16.0, 6.4 Hz)

Ejemplo de referencia 372-(2-(2-ciclopentilidimetil)-5-metiloxazol-4-il)etil)metansulfonato

IR ν (NaCl) cm^{-1} : 1631, 1545, 1506

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.45-1.85 (6H, br), 2.10-2.48 (2H, br), 2.26 (3H, s), 2.69-3.00 (2H, br), 2.66 (2H, t, J=6 Hz), 2.93 (3H, s), 4.46 (2H, t, J=6 Hz), 5.92 (1H, s)

Ejemplo de referencia 382-(2-(3-ciclopentilidimetil)-3-metiloxazol-4-il)etil)metansulfonato

IR ν (neat) cm^{-1} : 2957, 2979, 1659 1643, 1576, 1545, 1526

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.59-2.00 (4H, m), 2.27 (3H, s), 2.30-3.00 (4H, m), 2.67 (2H, t, J=6 Hz), 2.93 (3H, s), 4.46 (2H, t, J=6 Hz), 5.19-6.25 (1H, m)

Ejemplo de referencia 392-(2-(3-ter-butilmetiloxazol-trans-1-penten-1-il)-3-metiloxazol-4-il)etil)metansulfonato

IR ν (neat) cm^{-1} : 2981, 2929, 2862, 1641, 1576, 1535

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.32 (9H, s), 1.55-1.95 (2H, m), 2.18-2.40 (2H, m), 2.27 (3H, s), 2.57 (2H, t, J=7 Hz), 2.46 (2H, t, J=6 Hz), 2.94 (3H, s), 4.44 (2H, t, J=6 Hz), 5.19 (1H, d, J=16 Hz), 6.62 (1H, dt, J=16.0, 6.4 Hz)

Ejemplo de referencia 402-(2-(2-dimetilamino-trans-1-penten-1-il)-3-metiloxazol-4-il)etil)metansulfonato

IR ν (neat) cm^{-1} : 2941, 2862, 2810, 2775 1643 1533

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.40-1.90 (2H, m), 2.10-2.50 (4H, m), 2.22 (6H, s), 2.27 (3H, s), 2.66 (2H, t, J=6 Hz), 2.94 (3H, s), 4.43 (2H, t, J=6 Hz), 5.18 (1H, d, J=16 Hz), 6.63 (1H, dt, J=16.1, 6.4 Hz)

Ejemplo de referencia 412-(2-(4-metil-trans-1-penten-1-il)oxazol-4-il)etil)metansulfonato

IR ν (neat) cm^{-1} : 2959 2930 2872, 1661, 1597, 1549

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.95 (3H, d, J=6.4 Hz), 1.50-2.00 (1H, m), 1.14 (2H, t, J=6.8 Hz), 2.96 (3H, s), 2.94 (2H, t, J=6.7 Hz), 4.46 (2H, t, J=6.7 Hz), 6.21 (1H, d, J=16.0 Hz), 6.70 (1H, dt, J=16.0, 7.2 Hz), 7.40 (1H, s)

Ejemplo experimental 1

Utilizando ratones machos KK-A ^{y} que eran modelos de diabetes en forma espontánea, que habían desarrollado diabetes debido a la resistencia a la insulina, y que mostraban un alto contenido de glucosa en plasma,

hipertrigliceridemia o hiperinsulinemia, se ensayó la actividad farmacológica de los compuestos de ensayo

Método de ensayo

Se extrajo sangre en ayunas de la vena de la cola de ratones machos KK-A ^{y} , y se midieron los niveles de glucosa y triglicéridos en plasma, usando kits de ensayo disponibles comercialmente (ensayo de glucosa CII WARD y ensayo G de triglicéridos WARD, Wako Pure Chemical Industries, Ltd.) Los ratones se agruparon (5 ratones por grupo) en un grupo de control y un grupo de administración, de modo que la desviación promedio y estándar del peso corporal y los niveles de glucosa en plasma y de triglicéridos en plasma en cada grupo eran casi iguales. Los compuestos de ensayo (compuestos de los ejemplos 1, 2, 4, 5, 29, 22, 24, 27, 30, 33, 36, 37, 46, 43, 47, 52, 54, 58 y 64) se suspendieron en solución de goma arábiga al 5 % y se administraron (10 mg/kg/día) por vía oral al grupo de administración durante 4 días consecutivos. La solución de goma arábiga al 5 % se administró por vía oral al grupo de control. Se extrajo sangre en ayunas de la vena de la cola 24 horas después de la administración final y se midieron los niveles de glucosa y de triglicéridos en plasma. Se calculó la disminución de los niveles de glucosa y

triglicéridos en plasma a partir de la siguiente fórmula
Los resultados se indican en la tabla 1

Disminución (%) = [(promedio del grupo de control -
promedio del grupo de administración del compuesto de
ensayo) / promedio del grupo de control] x 100

Resultados

Tabla 1

Compuesto de ensayo	Disminución (%) en	
	el nivel de glucosa	el nivel de triglicéridos
Ejemplo 1	46,1	48,3
Ejemplo 2	40,3	40,5
Ejemplo 4	40,3	40,5
Ejemplo 5	57,2	71,1
Ejemplo 20	57,7	65,6
Ejemplo 22	45,3	51,4
Ejemplo 24	52,0	50,7
Ejemplo 27	53,4	54,8
Ejemplo 30	55,4	57,0
Ejemplo 33	56,2	68,3
Ejemplo 36	59,8	57,5
Ejemplo 37	53,2	56,1

mg/kg/día), de modo que la desviación promedio y estándar del peso corporal y los niveles de glucosa en plasma y de triglicéridos en plasma en cada grupo eran casi iguales. El compuesto de ensayo se suspendió en solución de metilcelulosa al 0,5 % y se administró por vía oral durante 2 semanas consecutivas a partir del día siguiente. La solución de metilcelulosa al 0,5 % se administró por vía oral al grupo de control. Se extrajo sangre en ayunas de la vena de la cola 24 horas después de la administración final y se midieron los niveles de glucosa y de triglicéridos en plasma. Se calculó la disminución de los niveles de glucosa y triglicéridos en plasma a partir de la siguiente fórmula. Los resultados se indican en la tabla 2.

Disminución (%) = [(promedio del grupo de control -
promedio del grupo de administración del compuesto de
ensayo) / promedio del grupo de control] x 100

Resultados

Tabla 2

Compuesto de ensayo	Disminución (%) en	
	el nivel de glucosa	el nivel de triglicéridos

Ejemplo 40	54,3	37,0
Ejemplo 45	39,7	32,0
Ejemplo 47	29,9	10,9
Ejemplo 52	26,6	19,1
Ejemplo 56	31,0	11,9
Ejemplo 58	25,1	23,2
Ejemplo 64	29,4	25,1

Ejemplo experimental 2

Usando ratones db/db que muestran genéticamente altos niveles de glucosa en plasma, hipertriglicéridemia, resistencia a la insulina y obesidad, se examinó la actividad farmacológica de los compuestos de ensayo de los ejemplos 1, 2 y 20.

Método de ensayo

Se extrajo sangre en ayunas de la vena de la cola de ratones machos db/db, se midieron los niveles de glucosa y triglicéridos en plasma, usando kits de ensayo disponibles comercialmente (ensayo de glucosa CII WARD y ensayo G de triglicéridos WARD, Wako Pure Chemical Industries, Ltd.). Los ratones se agruparon (6 ratones por grupo) en un grupo de control y en un grupo de administración del compuesto de ensayo (compuestos de los ejemplos 1, 2 y 20). (3

Ejemplo 1	21,3	62,7
Ejemplo 2	37,2	78,1
Ejemplo 20	54,6	72,0

Ejemplo experimental 3

Usando ratones ICR machos de 7 semanas de edad se examinó la toxicidad con una administración repetida.

Método de ensayo

Los ratones se agruparon (7 ratones por grupo) en un grupo de control y grupos de administración del compuesto de ensayo (compuestos de los ejemplos 2 y 20) (30 y 100 mg/kg/día), de modo que la desviación promedio y estándar del peso corporal de los ratones era casi la misma. El compuesto de ensayo se suspendió en solución de metilcelulosa al 0,5 % y se administró por vía oral durante 2 semanas consecutivas a partir del día siguiente. La solución de metilcelulosa de 0,5 % se administró por vía oral al grupo de control. 24 horas posteriores a la administración final, se administró Evans blue (100 µg/ratón) de la vena de la cola 5 minutos más tarde se extrajo sangre del plexo venoso orbital con anestesia. Usando sangre con EDTA, se midieron el valor de hematocrito y el recuento de eritrocitos. Usando el plasma, se midió la

concentración de Evans blue a partir del cual se calculó el volumen plasmático. Se eliminaron el hígado y el corazón y se midió el peso bruto.

Resultados

No se hallaron diferencias significativas en el peso corporal, el valor de hematocrito, el recuento de eritrocitos, el volumen plasmático, el peso del hígado y el corazón de los grupos de administración del compuesto de ensayo (compuestos de los ejemplos 2 y 20) (30 y 100 mg/kg/día) de aquéllas del grupo de control.

Ejemplo experimental 4

Usando ratas Wistar hembras de 8 semanas de edad, se examinó la toxicidad por administración repetida.

Método de ensayo

Las ratas se agruparon (8 ratas por grupo) en un grupo de control y grupos de administración del compuesto de ensayo (compuesto de los ejemplos 2 y 20) (30 y 100 mg/kg/día), de modo que la desviación promedio y estándar del peso corporal de las ratas era casi igual. El compuesto de ensayo se suspendió en solución de metilcelulosa al 0,5

% y se administró por vía oral durante 2 semanas consecutivas a partir del día siguiente. La solución de metilcelulosa al 0,5 % se administró por vía oral al grupo de control. Las ratas fueron dejadas en ayunas durante 18 horas a partir del último día de la administración. Se anestesiaron por administración intraperitoneal de pentobarbital sódico (50 mg/kg) 24 horas después de la administración final y se extrajo sangre. Usando sangre con EDTA, se midieron el valor de hematocrito y el recuento de eritrocitos, y usando suero, AST (GOT) y ALT (GPT). Además se eliminaron la grasa blanca alrededor del estómago, y el hígado y el corazón, y se midieron los pesos brutos de los mismos.

Resultados

No se hallaron diferencias significativas en el valor de hematocrito, el recuento de eritrocitos, el peso de la grasa blanca alrededor del estómago, y el hígado y el corazón, AST (GOT) y ALT (GPT) de los grupos de administración del compuesto de ensayo (compuesto de los ejemplos 2 y 20) (30 y 100 mg/kg/día) de aquéllas del grupo de control.

Ejemplo experimental 5

La superior hidrosolubilidad del compuesto de la presente invención se confirmó determinando la solubilidad del compuesto en agua.

Método de ensayo

El compuesto de ensayo pulverizado (compuestos de los ejemplos 2, 20, 22, 24, 27, 30, 40 ó 43, 25 mg) se agregó a un buffer (1,0 ml, pH 7.0) y la mezcla se agitó a 35°C durante 1 hora y se pasó a través de un filtro de membrana. La concentración del compuesto de ensayo en el filtrado se midió por cromatografía líquida de alto rendimiento. Los resultados se indican en la tabla 3.

Resultados

Tabla 3

Compuesto de ensayo	Solubilidad (mg/ml)
Ejemplo 2	10,0
Ejemplo 20	25 ó arriba
Ejemplo 22	25 ó arriba
Ejemplo 24	10.7
Ejemplo 27	25 ó arriba
Ejemplo 30	17.3
Ejemplo 40	10,7

Ejemplo 45

20,3

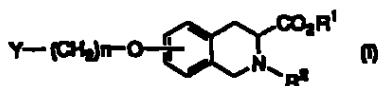
Aplicabilidad industrial

El nuevo compuesto heterocíclico que tiene la fórmula (I) antes mencionada de la presente invención y una sal farmacéuticamente aceptable del mismo tienen una acción hipoglucémica, una acción hipolipidémica en sangre, una acción que mejora la resistencia a la insulina y una acción que activa el PPAR α y son útiles como agente hipoglucémico, agente hipolipidémico, mejorador de la resistencia a la insulina, agente terapéutico de la diabetes, agente terapéutico de complicaciones diabéticas, mejorador de la tolerancia a la glucosa, agente antiarterioesclerosis, agente antiobesidad, agente antiinflamatorio, agente para la profilaxis o el tratamiento de enfermedades mediadas por el PPAR α y agente para la profilaxis o el tratamiento del síndrome X.

Esta aplicación se basa en la solicitud de patente n° 2001-161109 registrada en Japón, cuyos contenidos están incorporados en la presente por referencia.

Reivindicaciones

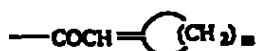
1 Un nuevo compuesto heterocíclico de la fórmula (I)



donde

R^1 es un átomo de hidrógeno o alquilo C_{1-4} ;

R^2 es un átomo de hidrógeno, $-\text{CO}-\text{R}^3$, donde R^3 es alquilo C_{1-4} opcionalmente sustituido por halógeno, $-\text{CO}-\text{C}(\text{R}^4)-\text{C}(\text{R}^4)-\text{R}^5$, donde R^4 es opcionalmente el mismo que el otro R^4 y es un átomo de hidrógeno o alquilo C_{1-4} , y R^5 es alquilo C_{1-4} , alquenilo C_{2-4} , arilo o un heterociclo aromático, $-\text{CO}-\text{C}=\text{C}-\text{R}^6$, donde R^6 es alquilo C_{1-4} ;



donde m es un número entero de 2 a 7, arilo, arilalquilo C_{1-4} opcionalmente sustituido, alquilo C_{1-4}

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donde k es un número entero de 2 a 7 y X es un átomo de oxígeno o un átomo de azufre, o

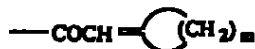
$\text{R}^{10}-\text{C}(\text{R}^{11})-\text{N}-\text{O}-$, donde R^{11} es un átomo de hidrógeno o alquilo C_{1-4} y R^{10} es arilo o un heterociclo aromático;

$Y-(CH_2)_n-O-$ está enlazado a la posición 6 ó 7 de un esqueleto de tetrahidroisoquinolina; y

n es un número entero de 1 a 4,

o una sal farmacéuticamente aceptable del mismo

2 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde, en la fórmula (I), R^1 es un arilalquilo C_{1-4} opcionalmente sustituido, alquilo C_{1-4} opcionalmente sustituido por halógeno, alquenilo C_{2-4} , cicloalquilo C_{3-4} , cicloalquil C_{3-4} -alquilo C_{1-3} o

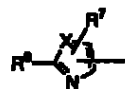


donde m es un número entero de 2 a 7, o una sal farmacéuticamente aceptable del mismo

3 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde, en la fórmula (I), Y es

opcionalmente sustituido por halógeno, alquenilo C_{2-4} , cicloalquilo C_{3-4} o cicloalquil C_{3-4} -alquilo C_{1-3} ;

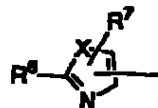
Y es



donde R^1 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es alquilo C_{1-4} , cicloalquilo C_{3-4} , alquilalquilo C_{1-4} -alquilo C_{1-3} , $\text{R}^{10}-\text{C}(\text{R}^{11})-\text{C}(\text{R}^{11})-$, donde R^{11} es opcionalmente el mismo que el otro R^{11} y es un átomo de hidrógeno o alquilo C_{1-4} y R^{10} es alquilo C_{1-4} opcionalmente sustituido por halógeno, alquenilo C_{2-4} , arilo o un heterociclo aromático, cicloalquilo C_{3-4} , cicloalquil C_{3-4} -alquilo C_{1-3} , alquil C_{1-4} -alquilo C_{1-4} , alquilalquilo C_{1-4} -alquilo C_{1-4} o alquilo C_{1-4} sustituido por $(\text{R}^{12})_2\text{N}-$, donde R^{12} es opcionalmente el mismo que el otro R^{12} y es un átomo de hidrógeno o alquilo C_{1-4} , $\text{R}^{10}-\text{CO}-\text{N}(\text{R}^{13})-$ donde R^{13} es un átomo de hidrógeno o alquilo C_{1-4} y R^{12} es alquilo C_{1-4} o arilo, $\text{R}^{13}-\text{X}-$, donde R^{13} es alquilo C_{1-4} o arilo y X es un átomo de oxígeno o un átomo de azufre, o



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donde R^1 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es alquilalquilo C_{1-4} -alquilo C_{1-3} , $\text{R}^{10}-\text{C}(\text{R}^{11})-\text{C}(\text{R}^{11})-$, donde R^{11} es opcionalmente el mismo que el otro R^{11} y es un átomo de hidrógeno o alquilo C_{1-4} , R^{10} es alquilo C_{1-4} opcionalmente sustituido por halógeno, cicloalquilo C_{3-4} , cicloalquil C_{3-4} -alquilo C_{1-3} , alquil C_{1-4} -alquilo C_{1-4} , alquilalquilo C_{1-4} -alquilo C_{1-4} o alquilo C_{1-4} sustituido por $(\text{R}^{12})_2\text{N}-$, donde R^{12} es opcionalmente el mismo que el otro R^{12} y es un átomo de hidrógeno o alquilo C_{1-4} , o



donde k es un número entero de 2 a 7, y X es un átomo de oxígeno o un átomo de azufre, o una sal farmacéuticamente aceptable del mismo

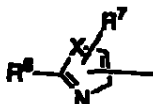
4 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1 donde, en la fórmula (I), R^1 es un átomo de hidrógeno, $-\text{CO}-\text{R}^3$, donde R^3 es alquilo C_{1-4} opcionalmente sustituido por halógeno, $-\text{CO}-\text{C}(\text{R}^4)-\text{C}(\text{R}^4)-\text{R}^5$, donde R^4 es opcionalmente el mismo que el otro R^4 y es un átomo de

hidrógeno o alquilo C_{1-4} y R^2 es alquilo C_{1-4} , alquénilo C_{2-4} , arilo o heterociclo aromático $-CO-C(R^2)-R^3$, donde R^3 es alquilo C_{1-4} , o arilo, y es



donde R^7 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es alquilo C_{1-4} , cicloalquilo C_{3-4} , $R^2-C(R^7)-C(R^7)-$, donde R^7 es opcionalmente el mismo que el otro R^7 y es un átomo de hidrógeno o alquilo C_{1-4} , R^3 es alquilo C_{1-4} , alquénilo C_{2-4} , arilo o heterociclo aromático, $R^3-CO-N(R^4)-$, donde R^4 es un átomo de hidrógeno o alquilo C_{1-4} , y R^3 es alquilo C_{1-4} o arilo, o R^3-Z- donde R^3 es alquilo C_{1-4} o arilo y Z es un átomo de oxígeno o un átomo de azufre, y X es un átomo de oxígeno o un átomo de azufre, o $R^3-C(R^4)-N-O-$, donde R^4 es un átomo de hidrógeno o alquilo C_{1-4} y R^3 es arilo o heterociclo aromático o una sal farmacéuticamente aceptable del mismo

8 El nuevo compuesto heterocíclico de acuerdo con las reivindicaciones 2 a 7, donde, en la fórmula (I), $Y-(CH_2)_n-O-$ está enlazado con la posición 7 del esqueleto de una tetrahidroisoquinolina y n es 2 o una sal farmacéuticamente aceptable del mismo



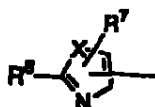
donde R^7 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es $R^2-C(R^7)-C(R^7)-$, donde R^7 es opcionalmente el mismo que el otro R^7 y es un átomo de hidrógeno o alquilo C_{1-4} y R^3 es cicloalquilo C_{3-4} , o una sal farmacéuticamente aceptable del mismo

9 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 8, donde, en la fórmula (I), Y es



donde R^7 es un átomo de hidrógeno o alquilo C_{1-4} y R^2 es alquilo C_{1-4} o cicloalquilo C_{3-4} , o una sal farmacéuticamente aceptable del mismo

10 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 9, donde, en la fórmula (I), Y es



11 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 4, donde, en la fórmula (I), $Y-(CH_2)_n-O-$ está enlazado con la posición 7 del esqueleto de una tetrahidroisoquinolina y n es 2 o una sal farmacéuticamente aceptable del mismo

12 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 6, donde, en la fórmula (I), Y es



donde R^7 es un átomo de hidrógeno o alquilo C_{1-4} , R^2 es $R^2-C(R^7)-C(R^7)-$, donde R^7 es opcionalmente el mismo que el otro R^7 y es un átomo de hidrógeno o alquilo C_{1-4} , y R^3 es alquilo C_{1-4} , alquénilo C_{2-4} o arilo, o una sal farmacéuticamente aceptable del mismo

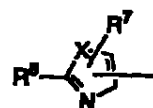
13 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 8, donde, en la fórmula (I), Y es

donde R^7 es un átomo de hidrógeno o alquilo C_{1-4} y R^2 es $R^2-C(R^7)-C(R^7)-$, donde R^7 es opcionalmente el mismo que el otro R^7 y es un átomo de hidrógeno o alquilo C_{1-4} y R^3 es cicloalquilo C_{3-4} , o una sal farmacéuticamente aceptable del mismo

14 El nuevo compuesto heterocíclico de acuerdo con cualquiera de las reivindicaciones 7 a 10, donde en la fórmula (I), R^2 es $-CO-C(R^2)-C(R^2)-R^4$, donde R^4 es un átomo de hidrógeno y R^3 es alquilo C_{1-4} o alquénilo C_{2-4} o una sal farmacéuticamente aceptable del mismo

15 El nuevo compuesto heterocíclico de acuerdo con cualquiera de las reivindicaciones 7 a 10, donde, en la fórmula (I), R^2 es $-CO-C(R^2)-R^4$, donde R^4 es alquilo C_{1-4} o una sal farmacéuticamente aceptable del mismo

16 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 6, donde en la fórmula (I), Y es



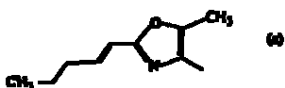
donde R' es alquilo C₁₋₄, R' es R''-C(R')-C(R')- donde R' es opcionalmente el mismo que el otro R' y es un átomo de hidrógeno o alquilo C₁₋₄, y R'' es alquilo C₁₋₄, y X es un átomo de oxígeno, o una sal farmacéuticamente aceptable del mismo

14 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 5, donde, en la fórmula (I), Y es

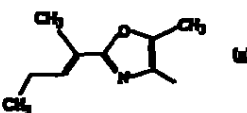
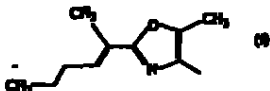
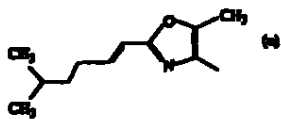
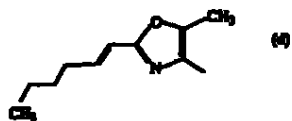
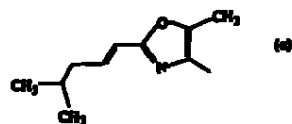
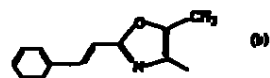
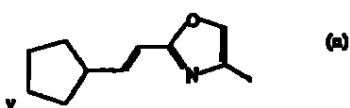
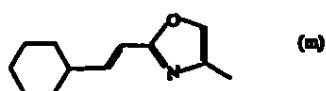
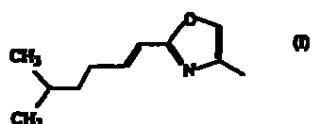
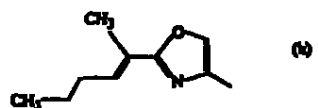
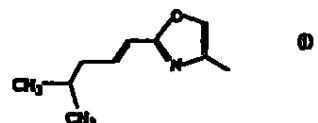
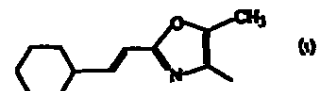
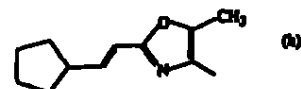


donde R' es alquilo C₁₋₄, R' es R''-C(R')-C(R')- donde R' es un átomo de hidrógeno y R'' es arilo, y X es un átomo de oxígeno, o una sal farmacéuticamente aceptable del mismo

15 El nuevo compuesto heterocíclico de acuerdo con las reivindicaciones 4 ó 5, donde, en la fórmula (I), Y está seleccionado de los siguientes (a) a (n):



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a una sal farmacéuticamente aceptable del mismo

16 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (16):

(1) Ácido 2-(2,4-hexadienil)-7-[2-(3-metil-2-estirilouazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carboxílico,

(2) Ácido 2-(2-heptenil)-7-[2-(3-metil-2-estirilouazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carboxílico,

(3) Ácido 2-(2-octenil)-7-[2-(3-metil-2-estirilouazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carboxílico,

(4) Ácido 7-[2-(3-metil-2-estirilouazol-4-il)etoxi]-2-pentafluoropropionil-1,2,3,4-tetrahidroisquinolin-(3H)-carboxílico,

(5) Ácido 2-(2-heptenil)-7-[2-(3-metil-2-estirilouazol-4-il)etoxi]-1,2,3,4-tetrahidroisquinolin-(3H)-carboxílico,

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(6) Ácido 2-(2,4-hexadienil)-7-[2-(5-metil-2-(1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(7) Ácido 2-(2-heptenil)-7-[2-(5-metil-2-(1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(8) Ácido 2-(2-hexilil)-7-[2-(5-metil-2-(1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(9) Ácido 2-(2,4-hexadienil)-7-[2-(5-metil-2-(1,3-pentadien-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(10) Ácido 2-(2,4-hexadienil)-7-[2-(5-metil-2-pentiloxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(11) Ácido 7-[2-(2-ciclopentil-5-metiloxazol-4-il)etoxi]-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(12) Ácido 7-[2-(2-ciclohexil-5-metiloxazol-4-il)etoxi]-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(13) Ácido 7-[2-(2-benzilaminotiazol-5-il)etoxi]-2-(2-heptenil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(14) Ácido 7-[2-(2-butilaminotiazol-5-il)etoxi]-2-(2-heptenil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(15) Ácido 2-(2-heptenil)-7-[2-(4-metil-2-feniloxazolidinotiazol-5-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico, y

(16) Ácido 2-(2-heptenil)-7-[2-(1-feniletilidaniminotiazol-5-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico, o una sal farmacéuticamente aceptable del mismo

17 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (3)

(1) Ácido 7-[2-(5-metil-2-estiriloxazol-4-il)etoxi]-2-pentafluoropropionil-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(2) Ácido 2-(2-heptenil)-7-[2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico, y

(3) Ácido 2-(2-hexilil)-7-[2-(5-metil-2-(trans-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico, o una sal farmacéuticamente aceptable del mismo

18 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (17):

(1) Ácido 2-(2,4-hexadienil)-7-[2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(2) Ácido 2-(2-heptenil)-7-[2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(3) Ácido 2-(2,4-hexadienil)-7-[2-(2-(1-hexen-1-il)-5-metiloxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(4) Ácido 2-(2,4-hexadienil)-7-[2-(5-metil-2-(5-metil-1-hexen-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(5) Ácido 2-(2,4-hexadienil)-7-[2-(5-metil-2-(1-metil-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico

(6) Ácido 2-(2,4-hexadienil)-7-[2-(5-metil-2-(1-metil-1-buten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(7) Ácido 2-(2-hexilil)-7-[2-(5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il)etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(8) Ácido 7-[2-(5-metil-2-(1-penten-1-il)oxazol-4-il)etoxi]-2-(2,3,3,3-pentafluoropropionil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carboxílico,

(9) Ácido 7-(2-[2-(4 4-dimetil-1-penten-1-il)-5-metiloxazol-4-il]etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(10) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(3-metil-1-buten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(11) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(2-(1-metilciclohexan-1-il)vinil)oxazol-4-il]etoxi)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(12) Ácido 7-(2-[2-(3,3-dimetil-1-buten-1-il)-5-metiloxazol-4-il]etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(13) Ácido 2-(2,4-hexadienoil)-7-[2-(2-(3-metoxi-1-propen-1-il)-5-metiloxazol-4-il]etoxi)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(14) Ácido 7-(2-[2-(2-ciclopentilvinil)-5-metiloxazol-4-il]etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(3) Ácido 2-(2-heptenoil)-7-[2-[3-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(4) Ácido 2-(2,4-hexadienoil)-7-[2-[2-(trans-1-hexen-1-il)-5-metiloxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(5) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(5-metil-trans-1-hexen-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(6) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(1-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(7) Ácido 2-(2,4-hexadienoil)-7-[2-[5-metil-2-(1-metil-trans-1-buten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico, y

(8) Ácido 2-(2-hexenoil)-7-[2-[3-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

a una sal farmacéuticamente aceptable del mismo

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(15) Ácido 7-(2-[2-(2-ciclohexilvinil)-5-metiloxazol-4-il]etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(16) Ácido 2-(2-butenil)-7-[2-[3-metil-2-(4-metil-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico y

(17) Ácido 7-(2-[5-metil-2-(4-metil-1-penten-1-il)oxazol-4-il]etoxi)-2-(4-pentenil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

o una sal farmacéuticamente aceptable del mismo

18 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (8)

(1) Ácido 2-(2 4-hexadienoil)-7-[2-(3-metil-2-(trans-1-penten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(2) Ácido 2-(2,4-hexadienoil)-7-[2-[3-metil-2-(4-metil-trans-1-penten-1-il)oxazol-4-il]etoxi]-1 2,3 4-tetrahidroisoquinolin-(3B)-carbonílico,

20 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1 donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (6)

(1) Ácido 7-(2-[3-metil-2-(trans-1-penten-1-il)oxazol-4-il]etoxi)-2-(2,2,3,3,3-pentafluoropropionil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(2) Ácido 7-(2-[2-(4,4-dimetil-trans-1-penten-1-il)-5-metiloxazol-4-il]etoxi)-2-(2,4-hexadienoil)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(3) Ácido 2-(2,4-hexadienoil)-7-[2-(5-metil-2-(3-metil-trans-1-buten-1-il)oxazol-4-il]etoxi]-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(4) Ácido 2-(2,4-hexadienoil)-7-[2-(3-metil-2-(2-trans-(1-metilciclohexan-1-il)vinil)oxazol-4-il]etoxi)-1,2,3,4-tetrahidroisoquinolin-(3B)-carbonílico,

(5) Ácido 7-(2-[2-(3,3-dimetil-trans-1-buten-1-il)-5-metiloxazol-4-il]etoxi)-2-(2,4-hexadienoil)-1 2,3 4-tetrahidroisoquinolin-(3B)-carbonílico, y

(6) Ácido 2-(2,4-hexadienil)-7-(2-(2-(3-metoxi-trans-1-propen-1-il)-5-metiloctanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

o una sal farmacéuticamente aceptable del mismo

21 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde el compuesto de la fórmula (I) son los siguientes (1) o (2):

(1) Ácido 7-(2-(2-(trans-2-ciclopentilvinil)-5-metiloctanil-4-il)etoxi)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

(2) Ácido 7-(2-(2-(trans-2-ciclohexilvinil)-5-metiloctanil-4-il)etoxi)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

o una sal farmacéuticamente aceptable del mismo

22 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde el compuesto de la fórmula (I) son los siguientes (1) o (2)

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(4) Ácido 2-(2-heptenil)-7-(2-(2-(4-metil-trans-1-pentan-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

(5) Ácido 2-(2-hexenil)-7-(2-(2-(4-metil-trans-1-pentan-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

(6) Ácido 2-(2,4-hexadienil)-7-(2-(2-(trans-1-hexen-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

(7) Ácido 2-(2,4-hexadienil)-7-(2-(2-(1-metil-trans-1-pentan-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

(8) Ácido 2-(2,4-hexadienil)-7-(2-(2-(1-metil-trans-1-butan-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico y

(9) Ácido 2-(2,4-hexadienil)-7-(2-(2-(3-metil-trans-1-hexen-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

o una sal farmacéuticamente aceptable del mismo

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(1) Ácido 2-(3-butenil)-7-(2-(2-(5-metil-2-(4-metil-trans-1-pentan-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

(2) Ácido 7-(2-(2-(3-metil-2-(4-metil-trans-1-pentan-1-il)octanil-4-il)etoxi)-2-(4-pentanil)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico

o una sal farmacéuticamente aceptable del mismo

23 El nuevo compuesto heterocíclico de acuerdo con la reivindicación 1, donde el compuesto de la fórmula (I) es cualquiera de los siguientes (1) a (9)

(1) Ácido 2-(2,4-hexadienil)-7-(2-(2-(4-metil-trans-1-pentan-1-il)octanil-4-il)etoxi)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

(2) Ácido 7-(2-(2-(trans-2-ciclopentilvinil)octanil-4-il)etoxi)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico

(3) Ácido 7-(2-(2-(trans-2-ciclohexilvinil)octanil-4-il)etoxi)-2-(2,4-hexadienil)-1,2,3,4-tetrahidroisquinolin-(38)-carboxílico,

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24 Una composición farmacéutica que contiene el nuevo compuesto heterocíclico de acuerdo con cualquiera de las reivindicaciones 1 a 23 o una sal farmacéuticamente aceptable del mismo

25 Un agente farmacéutico que contiene el nuevo compuesto heterocíclico de acuerdo con cualquiera de las reivindicaciones 1 a 23, o una sal farmacéuticamente aceptable del mismo, cuyo agente está seleccionado del grupo que consiste en un agente hipoglucémico, un agente hipolipídico, un mejorador de la resistencia a la insulina, un agente terapéutico de la diabetes, un agente terapéutico de complicaciones diabéticas, un mejorador de la tolerancia a la glucosa, un agente antiarterioesclerosis, un agente antiobesidad, un agente antiinflamatorio, un agente para la profilaxis o tratamiento de enfermedades mediadas por PPAR o un agente para la profilaxis o el tratamiento del síndrome X

26 Un método para la profilaxis o el tratamiento de diabetes complicación diabética hiperlipidemia arterioesclerosis, hiperglucemia, enfermedades causadas por la intolerancia a la glucosa resistente a la insulina enfermedades causadas por la resistencia a la insulina obesidad, inflamación, enfermedad mediada por PPAR o el síndrome X, que comprende la administración a un paciente

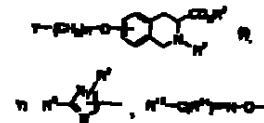
de una cantidad de eficacia farmacéutica del compuesto heterocíclico de acuerdo con cualquiera de las reivindicaciones 1 a 23 ó una sal farmacéuticamente aceptable del mismo

27 Uso de un nuevo compuesto heterocíclico de acuerdo con cualquiera de las reivindicaciones 1 a 23 ó una sal farmacéuticamente aceptable del mismo para la preparación de una composición farmacéutica para la profilaxis o el tratamiento de diabetes, complicación diabética, hiperlipidemia, arterioesclerosis, hiperglucemia, enfermedades causadas por la intolerancia a la glucosa resistente a la insulina, enfermedades causadas por la resistencia a la insulina, obesidad, inflamación, enfermedad mediada por PPAR o el síndrome X

antiinflamatorio, agente para la profilaxis o tratamiento de enfermedades mediadas por PPAR o agente para la profilaxis o el tratamiento del síndrome X

Resumen

El nuevo compuesto heterocíclico de la presente invención es un nuevo compuesto heterocíclico que tiene la fórmula (I)



donde R^1 es H o alquilo C_{1-4} , R^2 es H o $-CO-C(R^3)-C(R^4)-R^5$, donde R^3 es H o alquilo C_{1-4} y R^4 es alquilo C_{1-4} alquénilo C_{2-4} y similares y otros y es el siguiente grupo, donde X es O o S, R^6 es el mismo que R^1 , R^7 es $R^6-C(R^8)-C(R^9)-$ donde R^8 es el mismo que R^1 , R^{10} es C_{1-4} alquilo y similares, y otros, R^{11} es el mismo que R^1 y R^{12} es arilo y similares, $Y-CH_2CH_2-O-$ está enlazado a la posición 6 ó 7 del esqueleto de la tetrahidroisquinolina, y n es un número entero de 1 a 4, o una sal farmacéuticamente aceptable del mismo El compuesto (I) de la presente invención es útil como agente hipoglucémico, agente hipolipídico mejorador de la resistencia a la insulina, agente terapéutico de la diabetes, agente terapéutico de complicaciones diabéticas, mejorador de la tolerancia a la glucosa agente antiarterioesclerosis, agente antiobesidad agente

REQUISITOS NECESARIOS PARA PRESE TRAMITE

Radicacion : 81112006 00000000

Fecha (MM/AA): 2003-12-29 13:59:44

Tramite : 011 PCI-PAIENI 379 FOS. NACE 411 96 - 411A
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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USUARIO RADICADOR

PATENTE DE INVENCION

MODELO DE UTILIDAD

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- Indicación de que se solicita la concesion de una patente
- Datos de identificación del solicitante o de la persona que se presenta la solicitud
- Descripción de la invencion
- Dibujos de ser estos pertinentes
- Comprobante de Pago de las tasas establecidas

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DISEÑO INDUSTRIAL

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- Indicación de que se solicita el registro de Diseño Industrial
- Datos de identificación del solicitante o de la persona que presenta la solicitud
- Representacion grafica y fotografica del Diseño Industrial o muestra del Material que incorpora el diseño
- Comprobante de pago de las tasas establecidas

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ESQUEMA DE TRAZADO

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- Indicación de que solicita el registro de un Esquema de trazado
- Datos de identificación del solicitante o de la persona que presenta la solicitud
- Representacion grafica del esquema de trazado
- Comprobante de pago de las tasas establecidas

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Firma Responsable



Fecha



2020
Bogotá, D.C.,

Doctor:
MARGARITA CASTELLANOS A
Apoderado
KYOTO PHARMACEUTICAL INDUSTRIES LTD

Oficio N° 00732

ASUNTO:	Radicación N°	03-112806
	Solicitud Internacional	PCT/JP2002/05097
	Fecha Inicio fase nacional	29/12/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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:

□ El solicitante debe presentar un nuevo título que permita identificar la materia de la cual trata la solicitud, ya que el título relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 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 29 DEC 2004.

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