Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 05-96777

54 **TÍTULO** 1-2-4- Sustituyente-1,2-3-4-tetrahidro y 1,2- Dihidro Quinolina y Derivados E 1,2,3,4- tetrahidroQuinoxalina como inhibidores cetp para el tratamiento de Ateroesclerosis, y obesidad

51 **CLASIFICACIÓN INTERNACIONAL** A61K 31/47 A61P 3/04 A61K 31/4709

71 **SOLICITANTE** Pfizer Products Inc

DOMICILIO Eastern Point Road - Groton - Connecticut 06340 EUA

74 **APODERADO** Carlos R Olarte

22 **BOGOTÁ, D. C.,** Septiembre 22 - 2005

(FORMA P 10)

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA Y COMERCIO
Radicacion : 05096777
Fecha (MM): 2005-09-23 17:30:58
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES
Folios: 413

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 28-oct-05

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** PFIZER PRODUCTS INC **Dirección:** Eastern Point Road, Groton, Connecticut 06340 E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** Delaware, Estados Unidos de América. **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número _____
REPRESENTANTE APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número 79782747Bta TP 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA 1d103 **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB2004/000836 Fecha Marzo 15, 2004

Publicación Internacional No. WO 2004/085401 Fecha Octubre 7, 2004

(6) **Título (54)** 1, 2, 4-SUSTITUYENTE 1, 2, 3, 4-TETRAHIDRO Y 1, 2-DIHIDRO-QUINOLINA Y DERIVADOS E 1, 2, 3, 4-TETRAHIDROQUINOXALINA COMO INHIBIDORES CETP PARA EL TRATAMIENTO DE ATEROSCLEROSIS Y OBESIDAD.

Clasificación Internacional (51) C07D 215/14, 215/50, 215/12, 241/42, 401/04, 401/12, 409/12, 405/12, 413/12, 417/12, 403/06, 401/06, 413/06, 405/06/, 417/06. A61K31/47 ; A61P3/04 . A61K31/4709

Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 28, 2003	60/458,274

(9) **Comprobante de pago No.** 70.397 **Fecha** Septiembre 13, 2005

(10) **ANEX S**

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

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

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

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05096777 00000000 Folios: 413
Fecha (A'M'D): 2005-09-23 17:38:56
Tramite : 871 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 05 - 70,397
FECHA : SEPTIEMBRE 13 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00110-6	32743733	12/09/2005	3,647,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER PRODUCTS INC.

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

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb ejercía funciones de Vicepresidente de la Compañía Pfizer Products Inc., con sede en Groton, Connecticut, Estados Unidos.

Firma del notario

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

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

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

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210435
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Notaría Veintisiete de este Círculo hago constar que ésta Fotocopia coincide con su original que he tenido a la vista. 17 NOV 2003 NOTARIA VEINTISIETE EUGENIA ROJAS DE URUETA BOGOTA, D. C. - COLOMBIA

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

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

Marlen Neira C.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Power of Attorney

The undersigned,

Pfizer Products Inc.

domiciled in

Eastern Point Road, Groton, Connecticut 06340 USA

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

Poder

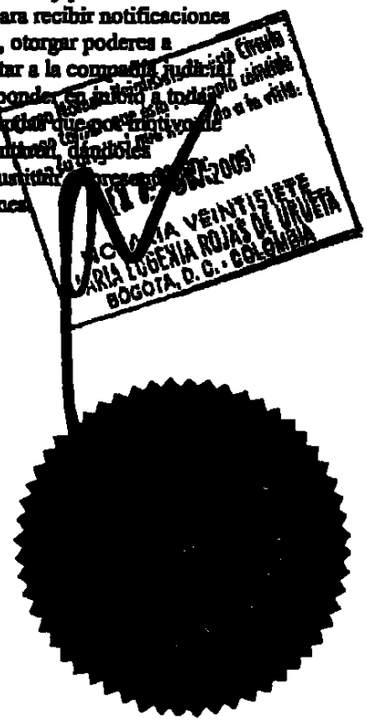
El suscrito,

Pfizer Products Inc.

domiciliado en

Eastern Point Road, Groton, Connecticut 06340 USA

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por intermedio de lo encomendado se presenten, dándoles asimismo facultad para sustituir [illegible] revocar dichas sustituciones.



Signature/Firma: _____

Date/Fecha: July 14, 2003

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

OLARTERAISBECK

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Notarial Certification

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

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

2. That the grantor has executed the foregoing document as Vice President of Pfizer Products Inc.

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

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

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

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

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

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

4. Que
con sede principal ubicada en

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

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

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

Como Notario Veintisiete de este Círculo hago constar que ésta fotocopia coincide con el original que he tenido a la vista.
NOTARIA VEINTISIETE
MARIA EUGENIA ROJAS DE URUETA
BOGOTA, D. C. - COLOMBIA

NOTARY PUBLIC (Signature):

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

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

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

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

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

Certified/Attesté

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

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

8. Number/sous No **G210435**

9. Stamp:
   timbre:

10. Signature: R. Bawden

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

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 October 2004 (07.10.2004)

PCT

(10) International Publication Number
WO 2004/085401 A1

(51) International Patent Classification[7]: C07D 215/14, 215/50, 215/12, 241/42, 401/04, 401/12, 409/12, 405/12, 413/12, 417/12, 403/06, 401/06, 413/06, 405/06, 417/06

(21) International Application Number:
PCT/IB2004/000836

(22) International Filing Date: 15 March 2004 (15.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/458,274 28 March 2003 (28.03.2003) US

(71) Applicant (*for all designated States except US*): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CHANG, George [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). DIDIUK, Mary, Theresa [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). FINNEMAN, Jarl, Ilmari [FI/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). GARIGIPATI, Ravi, Shankar [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). KELLEY, Ryan, Michael [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). PERRY, David, Austen [GB/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). RUGGERI, Roger, Benjamin [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). BECHLE, Bruce, Michael [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US).

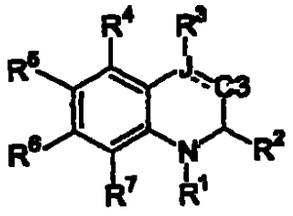
(74) Agents: LUMB, Trevor, J. et al.; c/o LAWRENCE, Jackie, Pfizer Inc., Mailstop 8260-1615, Eastern Point Road, Groton, CT 06340 (US).

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

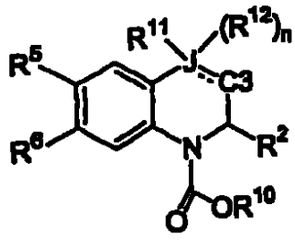
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Continued on next page]

(54) Title: 1,2,4-SUBSTITUERTE 1,2,3,4-TETRAHYDRO-AND 1,2 DIHYDRO-QUINOLINE AND 1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS CETP INHIBITORS FOR THE TREATMENT OF ATHEROSCLEROSIS AND OBESITY



(I)



(III)

(57) Abstract: Quinoline and quinoxaline compounds of formula I and III wherein the substituent are as defined in claims 1 and 15, pharmaceutical compositions containing such compounds and the use of such compounds to elevate certain plasma lipid levels, including high density lipoprotein-cholesterol and to lower certain other plasma lipid levels, such as LDL-cholesterol and triglycerides and accordingly to treat diseases which are exacerbated by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in some mammals, including humans.

WO 2004/085401 A1

Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

Published:

— *with international search report*

1,2,4-SUBSTITUERTE 1,2,3,4-TETRAHYDRO-AND 1,2 DIHYDRO-QUINOLINE AND 1,2,3,4-TETRAHYDRO-QUINOXALINE DERIVATIVES AS CETP INHIBITORS FOR THE TREATMENT OF ATHEROSCLEROSIS AND OBESITY

BACKGROUND OF INVENTION

This invention relates to quinoline and quinoxaline compounds, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein (HDL)-cholesterol and to lower certain other plasma lipid levels, such as low density lipoprotein (LDL)-cholesterol and triglycerides and accordingly to treat diseases which are affected by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in certain mammals (i.e., those which have CETP in their plasma), including humans.

Atherosclerosis and its associated coronary artery disease (CAD) is the leading cause of mortality in the industrialized world. Despite attempts to modify secondary risk factors (smoking, obesity, lack of exercise) and treatment of dyslipidemia with dietary modification and drug therapy, coronary heart disease (CHD) remains the most common cause of death in the U.S., where cardiovascular disease accounts for 44% of all deaths, with 53% of these associated with atherosclerotic coronary heart disease.

Risk for development of this condition has been shown to be strongly correlated with certain plasma lipid levels. While elevated LDL-C may be the most recognized form of dyslipidemia, it is by no means the only significant lipid associated contributor to CHD. Low HDL-C is also a known risk factor for CHD (Gordon, D.J., et al.,: "High-density Lipoprotein Cholesterol and Cardiovascular Disease", Circulation, (1989), 79: 8-15).

High LDL-cholesterol and triglyceride levels are positively correlated, while high levels of HDL-cholesterol are negatively correlated with the risk for developing cardiovascular diseases. Thus, dyslipidemia is not a unitary risk profile for CHD but may be comprised of one or more lipid aberrations.

Among the many factors controlling plasma levels of these disease dependent principles, cholesteryl ester transfer protein (CETP) activity affects all three. The role of this 70,000 dalton plasma glycoprotein found in a number of animal

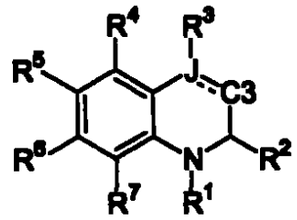
species, including humans, is to transfer cholesteryl ester and triglyceride between lipoprotein particles, including high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be pro-atherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD.

No wholly satisfactory HDL-elevating therapies are on the market today. Niacin can significantly increase HDL, but has serious toleration issues which reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL-C, but in some patients, the result is an increase of modest porportions (~10-12%). As a result, there is an unmet medical need for an approved therapeutic agent that elevates plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

Thus, although there are a variety of anti-atherosclerosis therapies, there is a continuing need and a continuing search in this field of art for alternative therapies.

SUMMARY OF THE INVENTION

This invention is directed to compounds according to Formula I



Formula I

Wherein

C3 is carbon;

J is nitrogen or carbon, wherein if J is carbon, then the bond between C3 and J is a single or double bond and if J is nitrogen, then the bond between C3 and J is a single bond;

R^1 is Y, W-X or W-Y^1; wherein W is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl; X is -O-Y, -S-Y, -N(H)-Y or -N-$(Y)_2$; Y for each occurrence is independently Z or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected

independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z; and Y^1 for each occurrence is independently Z or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z; wherein Z is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C_2-C_6)alkenyl, (C_1-C_6) alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent is also optionally substituted with from one to nine fluorines;

R^2 is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen and sulfur, and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully

saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen and sulfur, wherein said R^2 ring is optionally attached through (C_1-C_4)alkyl; wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, (C_2-C_8)alkenyl, (C_1-C_8) alkyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, oxo or (C_1-C_8)alkyloxycarbonyl;

R^3 is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain containing C4a, wherein C4a is a carbon atom that connects to J, wherein each carbon in the carbon chain may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen, and said carbon is optionally mono-, di- or tri-substituted with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is mono, di-, or tri-substituted with V at C4a or the R^3 carbon adjacent to C4a; provided that in R^3 , when J is carbon, it is other than C4a that is optionally replaced with one heteroatom; and provided that in R^3, when J is nitrogen, it is other than C4a that is optionally replaced with a heteroatom and it is other than C4a that is optionally mono-substituted with hydroxy or nitrogen; wherein V is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen such that V is not imidazolyl or a fully saturated heterocyclic nitrogen-containing ring wherein nitrogen of the ring is connected to the R^3 group; a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; or a tricyclic ring consisting of three fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with V^1, (C_1-C_8)alkyl-V^1, C(O)-V^1, O-(C_0-C_8)alkyl-V^1, (C_1-C_8)alkyl-O-V^1, C(O)-mono-N- or di-N,N-(C_1-C_8)alkyl-V^1, halo, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, hydroxy,

(C_1-C_8)alkoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, mono-N- or di-N,N-(C_1-C_8)alkylsulfonyl, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N-(C_1-C_8) alkylcarboxamoyl, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino, wherein said (C_1-C_8)alkyl or (C_2-C_8)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino, wherein each (C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfonyl or (C_2-C_8)alkenyl substituents are also optionally substituted with from one to nine fluorines; wherein V^1 is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V^1 substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with halo, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-substituted with oxo, said (C_1-C_8)alkyl or (C_1-C_8)alkoxy substituent is also optionally substituted with from one to nine fluorines; and

each of R^4, R^5, R^6 and R^7 are independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T or a partially saturated, fully saturated or fully unsaturated (C_1-C_{12}) straight or branched carbon chain wherein each carbon may optionally be replaced with one or two heteroatoms per carbon chain wherein the heteroatoms are selected independently from oxygen, sulfur and nitrogen, wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is optionally mono-substituted with T; wherein T is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen,

sulfur and oxygen; and said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino, said (C_1-C_8)alkyl or (C_1-C_8)alkoxy substituent also optionally has from one to nine fluorines;

R^4 and R^5, R^5 and R^6, and/or R^6 and R^7 may optionally be taken together and can form at least one ring that is a partially saturated or fully unsaturated four to eight membered ring optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein each ring formed by R^4 and R^5, or R^5 and R^6, and/or R^6 and R^7 is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_8)alkyl, (C_1-C_4)alkylsulfonyl, (C_2-C_8)alkenyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino, said (C_1-C_8)alkyl substituent also optionally has from one to nine fluorines;

or a pharmaceutically acceptable salt or prodrug thereof;

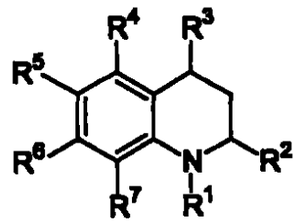
with the following provisos:

a) when there is a single bond between C3 and J, and R^3 is a fully saturated one to six membered straight or branched carbon chain substituted on C4a with V then R^1 is other than C(O)-(C_1-C_4)alkyl optionally mono-, di- or tri-substituted with halo and R^1 is other than C(O)-monocyclicaromatic ring; or

b) when there is a single bond between C3 and J, and R^3 is –C(O)-O-V, and R^2 is phenyl then R^1 is other than (C_1-C_4)alkyl; and

c) when there is a double bond between C3 and J, and R^2 is methyl then R^3 is other than -CH_2-O-V, –CH_2-V or –CH_2-CH_2-V.

Furthermore, the present invention is directed to compounds according to Formula II



Formula II

wherein

R^1 is W-X;

W is carbonyl;

X is –O-Y;

Y for each occurrence is independently (C_1-C_8)alkyl, said (C_1-C_8)alkyl optionally having one to nine fluorines or said (C_1-C_8)alkyl optionally mono-substituted with Z;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, nitro, cyano, oxo, or (C_1-C_4)alkyloxycarbonyl, said (C_1-C_4)alkyl optionally substituted with from one to nine fluorines;

R^2 is a partially saturated, fully saturated or fully unsaturated (C_1-C_4) straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one heteroatom selected independently from oxygen and sulfur wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo, said carbon is optionally mon-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo or (C_1-C_6)alkoxy;

wherein R^3 is $-CH_2NR^8R^9$ or $-C(O)NR^8R^9$;

wherein R^8 and R^9 are independently hydrogen or a (C_1-C_2) straight carbon chain wherein at least one of R^8 and R^9 are not hydrogen and wherein said carbon is

optionally mono-, di- or tri-substituted independently with halo, said carbon, other than the connecting carbon, is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, and said carbon chain is optionally mono, di-, or tri-substituted with V^3, wherein either R^8 or R^9 is substituted with V^3, or both R^8 and R^9 is substituted with V^3;

wherein V^3 is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said V^3 substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with V^4, (C_1-C_6)alkyl-V^4, C(O)-V^4, O-(C_0-C_6)alkyl-V^4, (C_1-C_6)alkyl-O-V^4, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, mono-N- or di-N,N-(C_1-C_6)alkylsulfonyl, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, wherein said (C_1-C_6)alkyl substituent is optionally mono-substituted with oxo, wherein said (C_1-C_6)alkyl substituent is optionally mono-substituted with hydroxy, said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituents are also optionally substituted with from one to nine fluorines;

wherein V^4 is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

wherein said V^4 substituent is optionally mono-, di-, tri-, or tetra-substituted independently with halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl substituent is optionally mono-substituted with oxo, said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent is also optionally substituted with from one to nine fluorines;

or wherein R^8 and R^9 are taken together to form a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to

four heteroatoms selected independently from oxygen, sulfur, and nitrogen or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, selected independently from nitrogen, sulfur and oxygen;

R^4 is hydrogen;

R^5 and R^6 are each independently hydrogen, halo, T, (C_1-C_8)alkoxy or (C_1-C_8)alkyl, said (C_1-C_8)alkoxy or (C_1-C_8)alkyl substituent optionally having from one to nine fluorines or said (C_1-C_8)alkoxy or (C_1-C_8)alkyl substituent optionally mono-substituted with T;

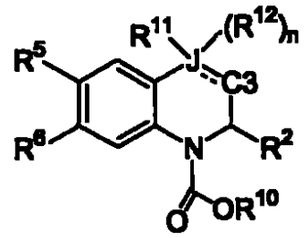
wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_8)alkyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent optionally has from one to nine fluorines;

R^7 is hydrogen;

or a pharmaceutically acceptable salt or prodrug thereof.

In addition, the present invention provides compounds of Formula III



Formula III

wherein

C3 is carbon;

J is carbon, wherein the bond between C3 and J is a single or double bond;

n is zero if the bond between C3 and J is a double bond or one if the bond between C3 and J is a single bond;

R^2 is (C_1-C_4)alkyl, cyclopropyl or cyclobutyl;

R^5 is CF_3;

R^6 is hydrogen;

R^{10} is a fully saturated (C_1-C_4) straight or branched carbon chain;

R^{11} is halo, hydroxy, –C(O)(O(C_1-C_4)alkyl), –C(O)C(O)(O(C_1-C_4)alkyl), –C(O)NH(O(C_1-C_4)alkyl), or –C(O)N((C_1-C_4)alkyl)(O(C_1-C_4)alkyl);

R^{12} is hydrogen or halo, wherein R^{11} is not halo when R^{12} is halo;

or R^{11} and R^{12} are taken together to form oxo or N_2;

or a pharmaceutically acceptable salt or prodrug thereof.

In addition, the present invention provides methods for treating atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal by administering to a mammal in need of such treatment an atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction treating amount of a compound of the present invention, or a pharmaceutically acceptable form of said compound.

In addition, the present invention provides pharmaceutical compositions which comprise a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable form of said compound and a pharmaceutically acceptable vehicle, diluent or carrier.

In addition, the present invention provides pharmaceutical compositions for the treatment of atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal which comprise a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable form of said compound and a pharmaceutically acceptable vehicle, diluent or carrier.

Moreover, the present invention provides pharmaceutical combination compositions comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a compound of the present invention, or a pharmaceutically acceptable form of said compound;

a second compound, said second compound being an HMG CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a PPAR modulator, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant (preferably an HMG-CoA reductase inhibitor, a PPAR modulator, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, rosuvastatin or pitavastatin); and a pharmaceutical vehicle, diluent or carrier. This composition may be used to treat the aforementioned diseases, including atherosclerosis.

Also, the present invention provides a kit for achieving a therapeutic effect in a mammal comprising packaged in association a first therapeutic agent comprising a therapeutically effective amount of a compound of claim 1, 8, 12, or 13, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, a second therapeutic agent comprising a therapeutically effective amount of an HMG CoA reductase inhibitor, a PPAR modulator, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant and a pharmaceutically acceptable carrier and directions for administration of said first and second agents to achieve the therapeutic effect.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of exemplary embodiments of the invention and the examples included therein.

Before the present compounds, compositions and methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods of making that may of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the present invention. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3- naphthoate)) salts.

The invention also relates to base addition salts of the compounds of the present invention. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of the present invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The chemist of ordinary skill will recognize that certain compounds of this invention will contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers and configurational isomers. All such isomers and mixtures thereof are included in this invention. Hydrates and solvates of the compounds of this invention are also included.

Where the compounds of the present invention possess two or more stereogenic centers and the absolute or relative stereochemistry is given in the name, the designations R and S refer respectively to each stereogenic center in ascending numerical order (1, 2, 3, etc.) according to the conventional IUPAC number schemes for each molecule. Where the compounds of the present invention possess one or more stereogenic centers and no stereochemistry is given in the name or structure, it is understood that the name or structure is intended to encompass all forms of the compound, including the racemic form.

The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof. The term "cis" refers to the orientation of two substituents with reference to each other and the plane of the ring (either both "up" or both "down"). Analogously, the term "trans" refers to the orientation of two substituents with reference to each other and the plane of the ring (the substituents being on opposite sides of the ring).

Alpha and Beta refer to the orientation of a substituent with reference to the plane of the ring. Beta is above the plane of the ring and Alpha is below the plane of the ring.

This invention also includes isotopically-labeled compounds, which are identical to those described by formulas I and II, except for the fact that one or more atoms are replaced by one or more atoms having specific atomic mass or mass numbers. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine, and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{15}O, ^{17}O, ^{18}F, and ^{36}Cl respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of the compounds or of the prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H), and carbon-14 (*i.e.*, ^{14}C), isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H), can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings:

As used herein, the term mammals is meant to refer to all mammals which contain CETP in their plasma, for example, rabbits and primates such as monkeys

and humans, including males and females. Certain other mammals e.g., dogs, cats, cattle, goats, sheep and horses do not contain CETP in their plasma and so are not included herein.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

By "pharmaceutically acceptable" is meant the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

"Compounds" when used herein includes any pharmaceutically acceptable derivative or variation, including conformational isomers (e.g., cis and trans isomers) and all optical isomers (e.g., enantiomers and diastereomers), racemic, diastereomeric and other mixtures of such isomers, as well as solvates, hydrates, isomorphs, polymorphs, tautomers, esters, salt forms, and prodrugs. By "tautomers" is meant chemical compounds that may exist in two or more forms of different structure (isomers) in equilibrium, the forms differing, usually, in the position of a hydrogen atom. Various types of tautomerism can occur, including keto-enol, ring-chain and ring-ring tautomerism. The expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form). Exemplary prodrugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of the present invention include but are not limited to those having a carboxyl moiety wherein the free hydrogen is replaced by (C_1-C_4)alkyl, (C_2-C_7)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

The following paragraphs describe exemplary ring(s) for the generic ring descriptions contained herein.

Exemplary five to six membered aromatic rings optionally having one or two heteroatoms selected independently from oxygen, nitrogen and sulfur include phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridiazinyl, pyrimidinyl and pyrazinyl.

Exemplary partially saturated, fully saturated or fully unsaturated five to eight membered rings optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen include cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and phenyl. Further exemplary five membered rings include 2H-pyrrolyl, 3H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathiolyl.

Further exemplary six membered rings include 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl.

Further exemplary seven membered rings include azepinyl, oxepinyl, and thiepinyl.

Further exemplary eight membered rings include cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings consisting of two fused partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen include indolizinyl, indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl,

cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

By "alkylene" is meant saturated hydrocarbon (straight chain or branched) wherein a hydrogen atom is removed from each of two adjacent carbons. Exemplary of such groups (assuming the designated length encompasses the particular example) are methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene).

By "halo" or "halogen" is meant chloro, bromo, iodo, or fluoro.

By "alkyl" is meant straight chain saturated hydrocarbon or branched chain saturated hydrocarbon. Exemplary of such alkyl groups (assuming the designated length encompasses the particular example) are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, neopentyl, tertiary pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl, isohexyl, heptyl and octyl.

"Alkenyl" referred to herein may be linear or branched, and they may also be cyclic (e.g. cyclobutenyl, cyclopentenyl, cyclohexanyl) or bicyclic or contain cyclic groups. They contain 1-3 carbon-carbon double bonds, which can be cis or trans.

By "alkoxy" is meant straight chain saturated alkyl or branched chain saturated alkyl bonded through an oxy. Exemplary of such alkoxy groups (assuming the designated length encompasses the particular example) are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, neopentoxy, tertiary pentoxy, hexoxy, isohexoxy, heptoxy and octoxy .

As used herein the term "mono-N-" or "di-N,N-(C_1-C_x)alkyl" refers to the (C_1-C_x)alkyl moiety taken independently when it is di-N,N-(C_1-C_x)alkyl (x refers to integers).

References (e.g., claim 1) to "said carbon" in the phrase "said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo" refers to each of the carbons in the carbon chain including the connecting carbon.

References to a "nitrogen... di-substituted with oxo" herein (e.g., claim 1) refer to a terminal nitrogen which constitutes a nitro functionality.

It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridyl" means 2-, 3- or 4-pyridyl, the term "thienyl" means 2- or 3-thienyl, and so forth.

DTT means dithiothreitol. DMSO means dimethyl sulfoxide. EDTA means ethylenediamine tetraacetic acid.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refer to a solvent or a mixture thereof which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

In one embodiment of formula I compounds of the present invention,

J is carbon;

R^1 is W-X;

W is carbonyl;

X is -O-Y;

Y for each occurrence is independently (C_1-C_8)alkyl, said (C_1-C_8)alkyl optionally having one to nine fluorines or said (C_1-C_8)alkyl optionally mono-substituted with Z;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, nitro, cyano, oxo, or (C_1-C_4)alkyloxycarbonyl, said (C_1-C_4)alkyl or (C_1-C_4)alkoxy is optionally substituted with from one to nine fluorines;

R^2 is beta and is a partially saturated, fully saturated or fully unsaturated (C_1-C_4) straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one heteroatom selected independently from oxygen and sulfur wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to

five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_6)alkoxy, amino, nitro, (C_1-C_4)alkyloxycarbonyl or carboxy;

wherein R^3 is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than C4a, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen, and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with cyano, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is optionally mono, di-, or tri-substituted with V at C4a or at the R^3 carbon adjacent to C4a; V is a three, four, five or six membered partially saturated, fully saturated or fully unsaturated ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen such that V is not imidazolyl or a fully saturated heterocyclic nitrogen-containing ring wherein nitrogen of the ring is connected to the R^3 group;

wherein said V ring is optionally mono-, di-, tri-, tetra- or penta-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, nitro, cyano or oxo, wherein said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines;

R^4 is hydrogen;

R^5 and R^6 are each independently hydrogen, halo, T, (C_1-C_6)alkoxy or (C_1-C_6)alkyl, said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally having from one to nine fluorines or said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein

said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines; and

R^7 is hydrogen.

In another embodiment of formula I compounds of the present invention,

Y is (C_1-C_4)alkyl, wherein said (C_1-C_4)alkyl substituent optionally has one to nine fluorines;

R^2 is (C_1-C_4)alkyl, cyclopropyl or cyclobutyl;

R^3 is –((C_1-C_4)alkyl)(NH_2)(V), –((C_1-C_3)alkyl)(NH(C_1-C_2)alkyl))(V), –((C_1-C_4)alkyl)(OH)(V), –((C_1-C_4)alkyl)(F)(V), –((C_1-C_2)alkyl)(O-C(O)(C_1-C_2)alkyl)(V), -C(O)-V, -C(OH)(C(O)O(C_1-C_3)alkyl)(V), -CF_2(V), -((C_1-C_2)alkyl)(NHC(O)(C_1-C_2)alkyl)(V), -CH_2(V), –((C_1-C_2)alkyl)(C(O)O(C_1-C_2)alkyl)(V), –((C_1-C_4)alkyl)(C(O)NH_2)(V),–((C_1-C_4)alkyl)(CN)(V), or–((C_1-C_3)alkyl)((C_1-C_3)alkoxy)(V),

V is phenyl optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, nitro, cyano or oxo wherein said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines;

R^5 and R^6 are each independently hydrogen, halo, (C_1-C_3)alkoxy or (C_1-C_3)alkyl, said (C_1-C_3)alkoxy optionally having from one to seven halo, said (C_1-C_3)alkyl optionally having from one to nine halo.

In a further embodiment of formula I compounds of the present invention,

Y is methyl, ethyl, 1-propyl, 2-propyl or tert-butyl;

R^2 is methyl, ethyl, 2-propyl, cyclopropyl or cyclobutyl;

R^3 is -C(O)-V, -C(OH)(C(O)OCH_3)(V), -CH(F)(V), -CF_2(V), -$CH(OCH_3)$(V), -CH(C(O)OCH_3)(V), -CH(CN)(V), -CH(OH)(V), -CH_2(V), -$CH(NH_2)$(V), -CH(NH(CH_3))(V), -CH(C(O)NH_2)(V), -$CH(CH_2OH)$V, -$CH(CH_2OCH_3)$V, -$CH(CH_2OC(O)CH_3)$V, -$CH(CH_2F)$V, or -$CH(CH_2NH_2)$V; and

V is phenyl optionally mono-, di- or tri-substituted independently with halo, nitro, or (C_1-C_2)alkyl, wherein said (C_1-C_2)alkyl optionally has from one to five fluorines;

R^5 and R^6 are each independently hydrogen, methyl, methoxy or chloro; said methoxy optionally having from one to three fluorines, said methyl optionally having from one to three fluorines.

In another embodiment of the present invention, formula I compounds include substituents wherein

Y is ethyl;

R^2 is ethyl or methyl;

R^3 is (3,5-bis-(trifluoromethyl)-phenyl)-hydroxy-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-cyano-methyl, 3,5-bis-trifluoromethyl-benzoyl; (3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl; (3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl; (3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl; (3,5-bis-(trifluoromethyl)-benzyl); (3,5-bis-trifluoromethyl-phenylcarbamoyl)-methyl; amino-(3,5-bis-(trifluoromethyl)-phenyl)-methyl; (3,5-bis-(trifluoromethyl)-phenyl)-methylamine-methyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-amino-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-fluoro-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-methoxy-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-hydroxy-ethyl; or 2-acetoxy-1-(3,5-bis-(trifluoromethyl)-phenyl)-ethyl;

R^5 is methoxy or trifluoromethyl; and

R^6 is hydrogen or methoxy.

In another embodiment of compounds of formula I, the bond between C3 and J is a single bond.

In yet another embodiment of compounds of formula I, the bond between C3 and J is a double bond.

In another embodiment, the compounds of formula I are selected from the group consisting of:

(*R, R, S*)-4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, S, S*)-4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, R*)-4-(3,5-bis-trifluoromethyl-benzyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methylaminomethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S, S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methylaminomethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-6,7-dimethoxy-2-methyl-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-6,7-dimethoxy-2-methyl-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, S, R*)- 4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl- methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, S, S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, R, R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[2-Acetoxy-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[2-Acetoxy-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-methoxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-methoxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-fluoro-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-fluoro-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-amino-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-amino-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,S*)-4-(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R*)-4-(3,5-bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S*)-4-(3,5-bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; and

(*R,R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment of compounds of formula I of the present invention,

J is nitrogen;

the bond between C3 and J is a single bond;

R^1 is W-X;

W is carbonyl;

X is –O-Y;

Y for each occurrence is independently (C_1-C_8)alkyl, said (C_1-C_8)alkyl optionally having one to nine fluorines or said (C_1-C_8)alkyl optionally mono-substituted with Z;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, nitro, cyano, oxo, or (C_1-C_4)alkyloxycarbonyl, said (C_1-C_4)alkyl or (C_1-C_4)alkoxy optionally substituted with from one to nine fluorines;

R^2 is a partially saturated, fully saturated or fully unsaturated (C_1-C_4) straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one heteroatom selected independently from oxygenand sulfur wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo,

said carbon is optionally monosubstituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygenand sulfur; wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_6)alkoxy, amino, nitro, (C_1-C_4)alkyloxycarbonyl or carboxy;

wherein R^3 is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than C4a or the R^3 carbon adjacent to C4a, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen, and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon, other than C4a, is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with cyano, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is optionally mono, di-, or tri-substituted with V at C4a or at the the R^3 carbon adjacent to C4a;

V is a five or six membered partially saturated, fully saturated or fully unsaturated ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen such that V is not imidazolyl or a fully saturated heterocyclic nitrogen-containing ring wherein nitrogen of the ring is connected to the R^3 group; wherein said V ring is optionally mono-, di-, tri-, tetra- or penta-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, nitro, cyano or oxo, wherein said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines;

R^4 is hydrogen;

R^5 and R^6 are each independently hydrogen, halo, T, (C_1-C_6)alkoxy or (C_1-C_6)alkyl, said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally having from one to nine fluorines or said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino,

oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl or (C_1-C_8)alkoxy substituent optionally has from one to nine fluorines;

R^7 is hydrogen.

In a further embodiment of compounds of formula I of the present invention,

Y is (C_1-C_4)alkyl, wherein said (C_1-C_4)alkyl substituent optionally has one to nine fluorines;

R^2 is (C_1-C_4)alkyl, cyclopropyl or cyclobutyl;

R^3 is -C(O)-V, -CH(C(O)O(C_1-C_3)alkyl)(V), or -CH(CN)(V);

V is phenyl optionally mono-, di- or tri-substituted independently with halo, (C_1-C_8)alkyl, hydroxy, (C_1-C_8)alkoxy, nitro, cyano or oxo wherein said (C_1-C_8)alkyl substituent optionally has from one to nine fluorines;

R^5 and R^6 are each independently hydrogen, (C_1-C_3)alkoxy or (C_1-C_8)alkyl, said (C_1-C_3)alkoxy optionally having from one to nine fluorines, said (C_1-C_8)alkyl optionally having from one to seven fluorines;

or a pharmaceutically acceptable salt thereof.

In a further embodiment of compounds of formula I of the present invention,

Y is methyl, ethyl, 1-propyl, 2-propyl or tert-butyl;

R^2 is methyl, ethyl, 2-propyl, cyclopropyl or cyclobutyl;

R^3 is 3,5-bis-trifluoromethyl-benzoyl, (3,5-bis-trifluoromethyl-phenyl)-cyano-methyl, or (3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl;

R^5 is methyl or trifluoromethyl;

R^6 is hydrogen or methyl.

In yet another embodiment of formula I compounds, the compound is selected from the group consisting of:

(*R*)-4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester; and

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt or prodrug thereof.

Moreover, one embodiment of the present invention includes a method for treating atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal by administering to a mammal in need of such treatment an atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction treating amount of a compound of formula I or II, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug.

In another embodiment, atherosclerosis is treated.

In another embodiment, peripheral vascular disease is treated.

In another embodiment, dyslipidemia is treated.

In another embodiment, hyperbetalipoproteinemia is treated.

In another embodiment, hypoalphalipoproteinemia is treated.

In another embodiment, familial-hypercholesterolemia is treated.

In another embodiment, coronary artery disease is treated.

In another embodiment, myocardial infarction is treated.

Furthermore, the present invention includes a pharmaceutical composition which comprises a therapeutically effective amount of a compound of formula I or II, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable vehicle, diluent or carrier.

In one embodiment, the present invention is a pharmaceutical composition for the treatment of atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal which comprises a therapeutically effective amount of a compound of formula I or II, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable vehicle, diluent or carrier.

In another embodiment, the present invention is a pharmaceutical composition for the treatment of atherosclerosis in a mammal which comprises an atherosclerosis treating amount of a compound of formula I or II, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable vehicle, diluent or carrier.

In another embodiment, the present invention includes a pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising: a first compound, said first compound being a compound of formula I or II, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; a second compound, said second compound being an HMG CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a PPAR modulator, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant; and a pharmaceutical vehicle, diluent or carrier.

In another embodiment, the present invention includes a pharmaceutical combination composition wherein the second compound is an HMG-CoA reductase inhibitor or a PPAR modulator.

In another embodiment, the present invention includes a pharmaceutical combination composition wherein the second compound is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, rosuvastatin or pitavastatin.

In another embodiment, the present invention includes a pharmaceutical combination composition further comprising a cholesterol absorption inhibitor. In another embodiment, the cholesterol absorption inhibitor is ezetimibe.

One further embodiment of the present invention includes a method for treating atherosclerosis in a mammal comprising administering to a mammal in need of treatment thereof; a first compound, said first compound being a compound of formula (I), a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and a second compound, said second compound being an HMG CoA reductase inhibitor, a PPAR modulator, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant; wherein the amounts of first and second compounds result in a therapeutic effect.

In another embodiment, the present invention includes a method for treating atherosclerosis wherein the second compound is an HMG-CoA reductase inhibitor or a PPAR modulator.

In another embodiment, the present invention includes a method for treating atherosclerosis wherein the second compound is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, rosuvastatin or pitavastatin.

In another embodiment, the present invention includes a method for treating atherosclerosis wherein the method further comprises administering a cholesterol absorption inhibitor. In another embodiment, the cholesterol absorption inhibitor is ezetimibe.

A further embodiment of the present invention includes a kit for achieving a therapeutic effect in a mammal comprising packaged in association a first therapeutic agent comprising a therapeutically effective amount of a compound of claim 1, 8, 12, or 13, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, a second therapeutic agent comprising a therapeutically effective amount of an HMG CoA reductase inhibitor, a PPAR modulator, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of

niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant and a pharmaceutically acceptable carrier and directions for administration of said first and second agents to achieve the therapeutic effect.

In another embodiment, the present invention includes a kit wherein said second compound is an HMG-CoA reductase inhibitor or a PPAR modulator.

In a further embodiment, the present invention includes a kit wherein said second compound is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, rosuvastatin or pitavastatin.

In another embodiment, the present invention includes a kit that further comprises a cholesterol absorption inhibitor. In another embodiment, the cholesterol absorption inhibitor is ezetimibe.

Specific compounds of formula III include:

2-Ethyl-4-iodo-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

2-Ethyl-4-iodo-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

4-Chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

4-Bromo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

4-Diazo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

4-Chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1,4-dicarboxylic acid 1-ethyl ester 4-methyl ester;

2-Ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4-methyl ester;

2-Ethyl-4-(methoxy-methyl-carbamoyl)-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

2-Ethyl-6-trifluoromethyl-2H-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4-methyl ester;

4-Chloro-2-ethyl-4-methoxycarboncarbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

2-Ethyl-4-methoxycarboncarbonyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid-ethyl ester;

4-Diazo-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

6,7-Dimethoxy-4-methoxycarboncarbonyl-2-methyl- 2H-quinoline-1-carboxylic acid-ethyl ester;

6,7-Dimethoxy- 2-methyl- 3,4-dihydro-2H-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4-methyl ester;

6,7-Dimethoxy-4-(methoxy-methyl-carbamoyl)-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

2-Ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid methyl ester;

2-Ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid methyl ester;

2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 1-propyl ester;

2-Ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 1-propyl ester;

2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-propyl ester;

2-Ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 2-propyl ester;

2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid *tert*-butyl ester;

2-Ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid *tert*-butyl ester; and

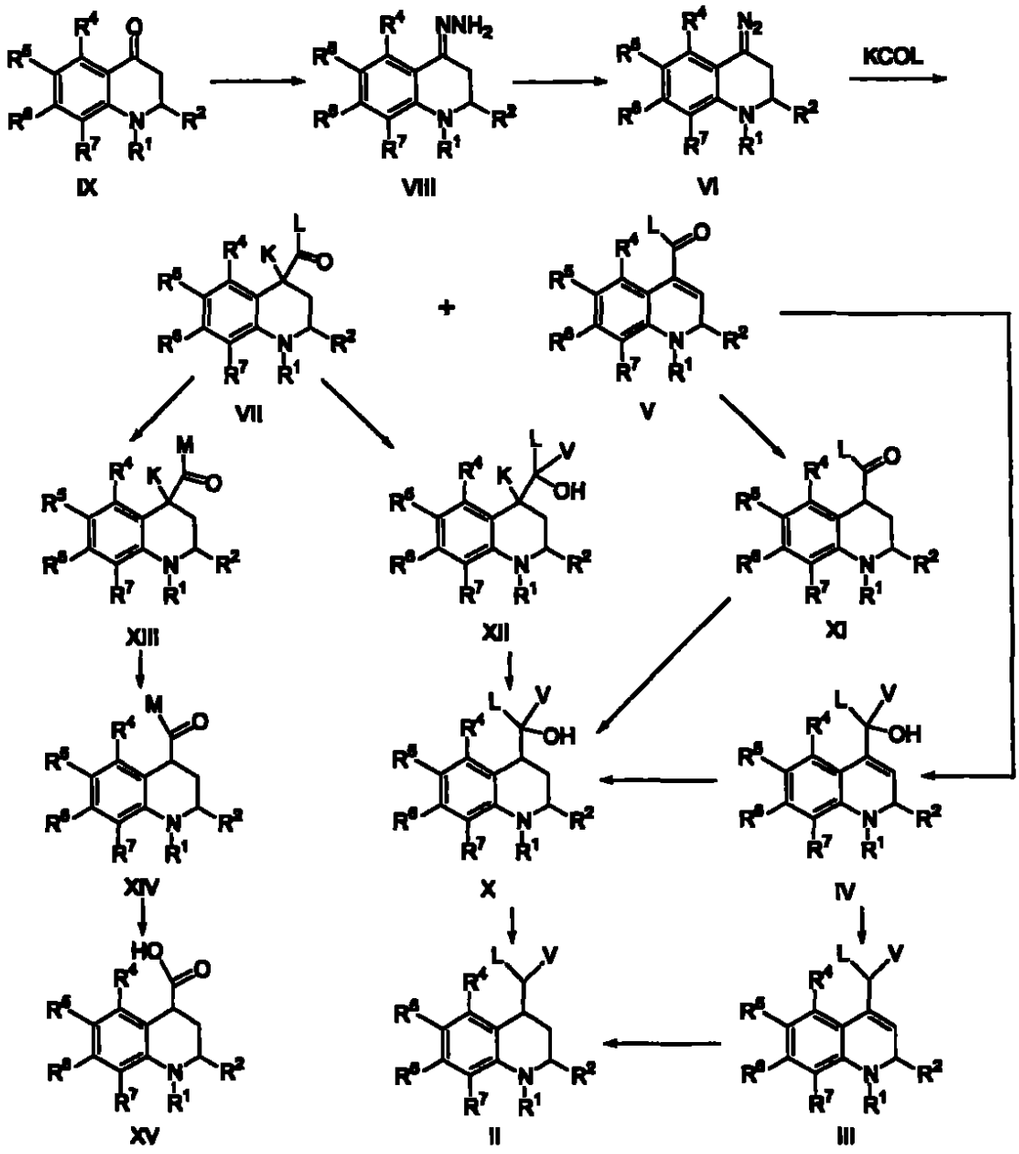
2-Ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4-methyl ester.

In general, the compounds of this invention can be made by processes which include processes analogous to those known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of this invention are provided as further features of the invention and are illustrated by the following reaction schemes. Other processes may be described in the experimental section. Analogous processes are disclosed in the following U.S.

patents, which are hereby incorporated by reference herein in their entirety: U.S. Patent 6,140,342; U.S. Patent 6,362,196; U.S. Patent 6,147,090; U.S. Patent 6, 395,751; U.S. Patent 6,147,089; U.S. Patent 6,310,075; U.S. Patent No. 6,197,786; U.S. Patent 6,140,343; U.S. Patent 6,489,478; and International Publication No. WO 00/17164.

The Reaction Schemes herein described are intended to provide a general description of the methodology employed in the preparation of many of the Examples given. However, it will be evident from the detailed descriptions given in the Experimental section that the modes of preparation employed extend further than the general procedures described herein. In particular, it is noted that the compounds prepared according to these Schemes may be modified further to provide new Examples within the scope of this Invention. For example, an ester functionality may be reacted further using procedures well known to those skilled in the art to give another ester, an amide, a carbinol or a ketone.

SCHEME 1



SCHEME 1

According to reaction Scheme 1, the desired compounds wherein J is carbon, the optional double bond is absent, R^3 is a group CH(V)(L) wherein L is a (C_1-C_6) alkoxycarbonyl group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above (depicted in Scheme 1 as Formula II compounds) may be prepared as a mixture of diastereoisomers from the corresponding Scheme 1, Formula III compounds by reduction of the double bond or L is R^3 as defined herein. This may

be achieved by hydrogenation in a reaction inert solvent such as methanol, ethanol or acetic acid with a catalyst such as palladium or rhodium on carbon under a hydrogen pressure equal to 15-50 psi for a period between 2-24hrs, or by transfer hydrogenation using ammonium formate in refluxing methanol in the presence of a catalyst such as palladium on carbon in a reaction inert solvent such as methanol or ethanol at a temperature between 0°C to 80°C, typically 25°C to 60°C. This method of preparing these particular Formula I compounds typically provides a preponderance of those diastereoisomers in which the R^2 and R^3 groups are *cis* to one another.

The desired Formula III compounds wherein L, V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula IV compounds by removal of the hydroxyl group. This may be achieved by treatment with a chlorinating agent such as phosphorus (III) chloride or thionyl chloride in a reaction inert solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, typically ambient, for a period between 1 to 24hr. The chloro-derivative thus formed is then treated with a finely divided metal such as zinc in the presence of an acid, or mixture of acids, such as acetic acid or hydrochloric acid in a suitable solvent, or mixture of solvents such as methanol, water or tetrahydrofuran at a temperature between 25°C to 60°C, typically ambient, to provide the desired product of Formula III.

The desired Formula IV compounds wherein L is a (C_1-C_6) alkoxycarbonyl group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula V compounds by reaction with a suitable organometallic derivative of the V group such as a magnesium or lithium derivative, prepared in turn from a compound V-Hal where Hal represents a chlorine, bromine or iodine atom, using methods well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. This reaction is conducted in a suitable reaction inert solvent such tetrahydrofuran or diethyl ether at a temperature between -78°C to 25°C, typically -78°C, to provide the desired product of Formula IV.

The desired Formula V compounds wherein L is a (C_1-C_6) alkoxycarbonyl group and R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from

the corresponding Formula VI compounds by reaction with an acyl compound KCOL wherein K is a leaving group such as chlorine or bromine, at a temperature between 0°C to 25°C, typically ambient, in a reaction inert solvent such as acetonitrile or toluene optionally in the presence of a base such as diisopropylethylamine or triethylamine to remove traces of HK which may be present. Depending on the nature of the substitutents on the Formula VI compounds and the nature of L, the Formula V compound may be obtained as a mixture with the corresponding Formula VII compound.

The desired Formula VI compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula VIII compounds by reaction with a suitable oxidizing agent, typically manganese (IV) oxide, in a suitable reaction inert solvent such as diethyl ether at a temperature between 0°C to 25°C, typically ambient. Since this reaction produces an equivalent of water, which may be deleterious in the subsequent step, this may optionally be removed by addition of a solvent suitable for the next reaction such as acetonitrile or toluene and evaporation of the solvent mixture to a volume somewhat less than that of the added solvent, but not to dryness.

The desired Formula VIII compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula IX compounds by reaction with hydrazine hydrate in a suitable reaction inert solvent such as ethanol or toluene at a temperature between 25°C to 180°C, typically 80°C to 170°C. The hydrazone formation may be assisted by continuous removal of water, such as by the use of a Dean-Stark apparatus, or by heating in a closed vessel to a temperature beyond the boiling point of the solvent such as by a microwave oven.

An alternative preparation of the desired Formula II compounds wherein L is a (C_1-C_6) alkoxycarbonyl group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be accomplished from the corresponding Formula X compounds by treatment with a chlorinating agent such as phosphorus (III) chloride or thionyl chloride in a reaction inert solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, typically ambient, for a period between 1 to 24hr. The chloro-derivative thus formed as a mixture of diastereoisomers is then treated with a finely divided metal such as zinc in the presence of an acid, or mixture of acids, such as acetic acid or hydrochloric acid in a

suitable solvent, or mixture of solvents such as methanol, water or tetrahydrofuran at a temperature between 25°C to 60°C, typically ambient, to provide the desired product of Formula II.

The desired Formula X compounds wherein L is a (C_1-C_8) alkoxycarbonyl group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula XI compounds by reaction with a suitable organometallic derivative of the V group such as a magnesium or lithium derivative, prepared in turn from a compound V-Hal where Hal represents a chlorine, bromine or iodine atom, using methods well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. This reaction is conducted in a suitable reaction inert solvent such tetrahydrofuran or diethyl ether at a temperature between -78°C to 25°C, typically -78°C, to provide the desired product of Formula X.

The desired Formula XI compounds wherein L is a (C_1-C_8) alkoxycarbonyl group and R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula V compounds by reduction of the double bond. This may be achieved by hydrogenation in a reaction inert solvent such as methanol, ethanol or acetic acid with a catalyst such as palladium or rhodium on carbon under a hydrogen pressure equal to 15-50 psi for a period of 2-24hrs, or by transfer hydrogenation using ammonium formate in refluxing methanol in the presence of a catalyst such as palladium on carbon in a reaction inert solvent such as methanol or ethanol at a temperature between 0°C to 80°C, typically 25°C to 60°C.

An alternative preparation of the desired Formula X compounds wherein L is a (C_1-C_8) alkoxycarbonyl group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula XII compounds, wherein K is a leaving group such as chlorine or bromine, by hydrogenation in a reaction inert solvent such as methanol, ethanol or acetic acid with a catalyst such as palladium or rhodium on carbon under a hydrogen pressure equal to 15-50 psi for a period between 2-24hrs, or by transfer hydrogenation using ammonium formate in refluxing methanol in the presence of a catalyst such as palladium on carbon in a reaction inert solvent such as methanol or ethanol at a

temperature between 0°C to 80°C, typically 25°C to 60°C to provide the desired product of Formula X.

Another alternative preparation of the desired Formula X compounds wherein L is a (C_1-C_8) alkoxycarbonyl group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula IV compounds by reduction of the double bond. This may be accomplished by hydrogenation in a reaction inert solvent such as methanol, ethanol or acetic acid with a catalyst such as palladium or rhodium on carbon under a hydrogen pressure equal to 15-50 psi for a period between 2-24hrs, or by transfer hydrogenation using ammonium formate in refluxing methanol in the presence of a catalyst such as palladium on carbon in a reaction inert solvent such as methanol or ethanol at a temperature between 0°C to 80°C, typically 25°C to 60°C to provide the desired product of Formula X. An alternative method of reduction involves treatment with diimide which is generated in situ in a reaction-inert solvent in the presence of the Formula IV compounds by a number of methods known to those skilled in the arts, such as those described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995.

The desired Formula XII compounds wherein L is a (C_1-C_8) alkoxycarbonyl group, K is a leaving group such as chlorine or bromine, and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula VII compounds by reaction with a suitable organometallic derivative of the V group such as a magnesium or lithium derivative, prepared in turn from a compound V-Hal where Hal represents a chlorine, bromine or iodine atom. This reaction is conducted in a suitable reaction inert solvent such tetrahydrofuran or diethyl ether at a temperature between -78°C to 25°C, typically -78°C, to provide the desired product of Formula XII.

As referred to above, the desired Formula VII compounds wherein L is a (C_1-C_8) alkoxycarbonyl group, K is a leaving group such as chlorine or bromine, and R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula VI compounds by reaction with an acyl compound KCOL at a temperature between 0°C to 25°C, typically ambient, in a reaction inert solvent such as acetonitrile or toluene, optionally in the presence of a base such as diisopropylethylamine or triethylamine to remove traces of HK which may be present. Depending on the nature of the substituents on the Formula VI

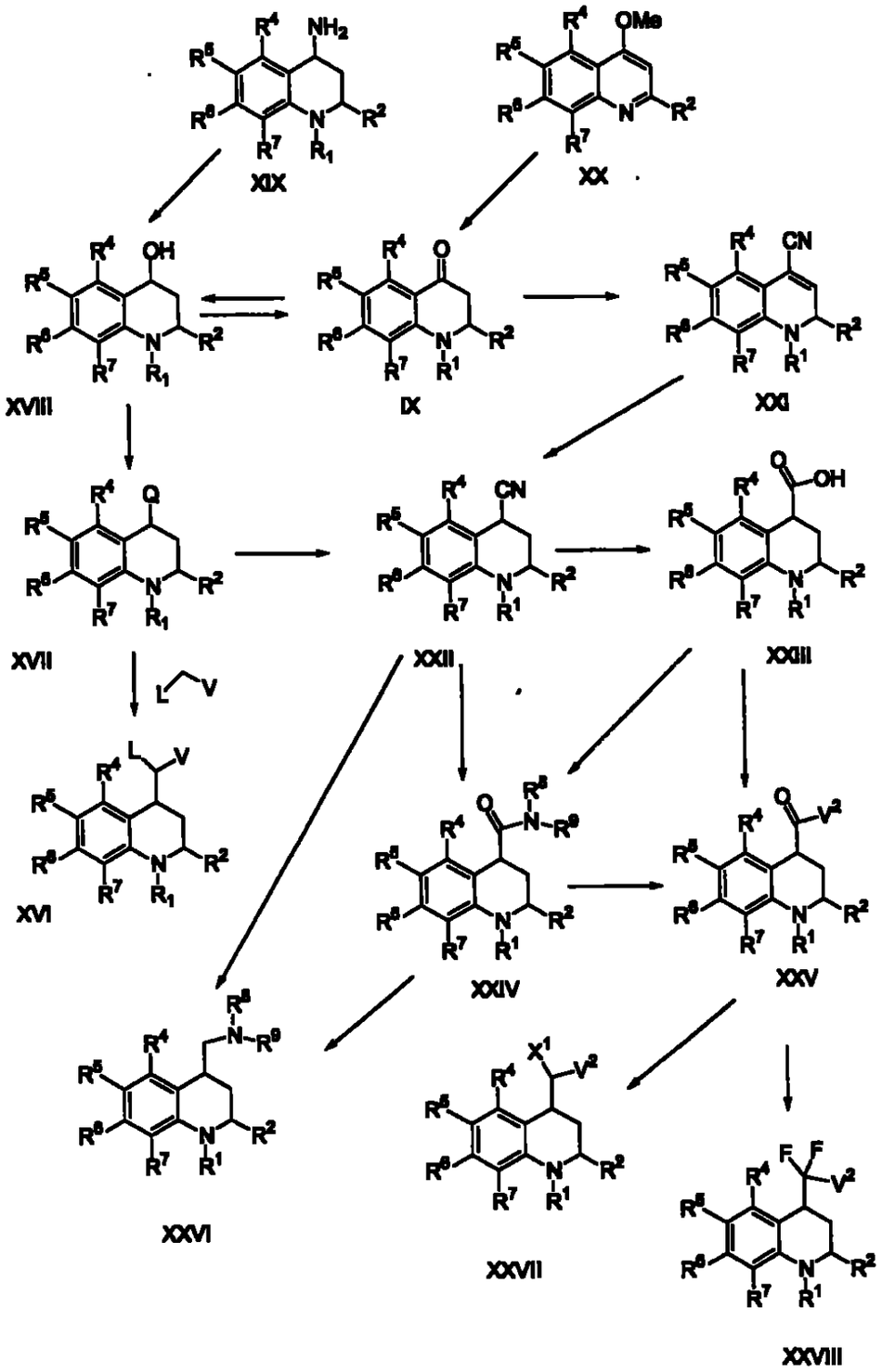
compounds and the nature of L, the Formula VII compound may be obtained as a mixture with the corresponding Formula V compound.

The desired Formula XIII compounds wherein M is a (C_1-C_6) alkoxy group and R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula VI compounds by reaction with phosgene at a temperature between 0°C to 25°C, typically ambient, in a reaction inert solvent such as acetonitrile or toluene in the presence of a base such as diisopropylethylamine or triethylamine. Addition of the desired alcohol MOH to the acid chloride in the presence of excess base then provides the desired Formula XIII compound.

The desired Formula XIV compounds wherein M is a (C_1-C_6) alkoxy group and R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula XIII compounds by hydrogenolysis. This may be achieved by hydrogenation in a reaction inert solvent such as methanol, ethanol or acetic acid with a catalyst such as palladium or rhodium on carbon under a hydrogen pressure equal to 15-50 psi for a period between 2-24hrs, or by transfer hydrogenation using ammonium formate in refluxing methanol in the presence of a catalyst such as palladium on carbon in a reaction inert solvent such as methanol or ethanol at a temperature between 0°C to 80°C, typically 25°C to 60°C. Alternatively, the Formula XIII compounds may be treated with a finely divided metal such as zinc in the presence of an acid, or mixture of acids, such as acetic acid or hydrochloric acid in a suitable solvent, or mixture of solvents such as methanol, water or tetrahydrofuran at a temperature between 25°C to 60°C, typically ambient, to provide the desired Formula XIV compounds.

The desired Formula XV compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared by hydrolysis of the ester group of the Formula XIV compounds, using methods well known to those skilled in the arts, such as can be found in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, for example, by treatment with an aqueous base, preferably, lithium, sodium, or potassium hydroxide, in a polar solvent, preferably dioxane, at a temperature between 0°C and 100°C (preferably room temperature) for between 1 to 20 hours to provide the desired Formula XV compounds.

SCHEME 2


XIX
XX
XVIII
IX
XXI
XVII
XXII
XXIII
XVI
XXIV
XXV
XXVI
XXVII
XXVIII

SCHEME 2

According to reaction Scheme 2, the desired compounds wherein J is carbon, the optional double bond is absent, R^3 is a group CH(V)(L) wherein L is a (C_1-C_6) alkoxycarbonyl group or a cyano group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above (depicted as Formula XVI compounds) may be prepared as a mixture of diastereoisomers from the corresponding Formula XVII compounds by reaction with a compound VCH_2L in the presence of a suitable base such as 1,8-diazabicyclo[5.4.0]undec-7-ene , diisopropylethylamine, triethylamine or sodium hydride in a reaction inert solvent such as N,N-dimethylformamide, dimethylsulfoxide, acetonitrile or toluene at a temperature between 0°C to 60°C, typically ambient.

The desired Formula XVII compounds wherein Q is a leaving group such as chlorine, bromine, methanesulfonyloxy or p-toluenesulfonyloxy and R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula XVIII compounds by reaction with the appropriate reagent such as methanesulfonyl chloride or toluenesulfonyl chloride in the presence of a suitable base such as diisopropylethylamine or triethylamine in a reaction inert solvent such as N,N-dimethylformamide, dimethylsulfoxide, chloroform, methylene chloride or toluene at a temperature between 0°C to 60°C, typically ambient. Other suitable reagents for formation of the Formula XVII compounds include phosphorus (III) chloride, phosphorus (III) bromide and thionyl chloride optionally in a reaction inert solvent such as chloroform, methylene chloride, pyridine or toluene at a temperature between 0°C to 60°C, typically ambient.

The desired Formula XVIII compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared as a mixture of diastereoisomers from the corresponding Formula IX compounds by reduction of the carbonyl group using methods and reagents well known to those skilled in the arts, such as can be found in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichestar, England, 1995, for example using sodium borohydride in an alcohol solvent such as methanol of ethanol at a temperature between 0°C to 60°C, typically ambient or using potassium tri-sec-butylborohydride (K-Selectride®) in a reaction inert solvent such as tetrahydrofuran or diethyl ether at a temperature between -78°C to 25°C, typically 0°C.

In an alternative procedure, the desired Formula XVIII compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be obtained by treatment of the corresponding Formula XIX compounds with sodium nitrite in the presence of an

acid, preferably acetic acid, followed by hydrolysis with a suitable base such as lithium, sodium, or potassium hydroxide, preferably sodium hydroxide in a suitable hydroxylic solvent such as ethanol to give the desired Formula XIX compounds. Methods for the preparation of Formula XIX compounds are described in US Patent 6197786 and International Application WO 0140180.

The desired Formula IX compounds wherein R^1 is an alkoxycarbonyl group and R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding 4-methoxyquinoline compounds of Formula XX by treatment with an organomagnesium derivative of the R^2 group together with an acylating agent such as ethyl chloroformate at a temperature between -100°C to 70°C, typically -78°C in a reaction inert solvent such as tetrahydrofuran followed by warming to a temperature between 0°C and about 70°C (preferably ambient) for between 0.1 and 24hr, preferably 1hr, followed by hydrolysis in aqueous acid, preferably 1N hydrochloric acid to give the desired Formula IX compounds, as described in US Patent 6197786.

In an alternative procedure, the desired Formula IX compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be obtained by oxidation of the corresponding Formula XVIII compounds using a variety of methods and reagents well known to those skilled in the arts, such as can be found in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, for example pyridinium chlorochromate, aqueous sodium hypochlorite in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) free radical and catalytic potassium bromide in a suitable reaction inert solvent such as methylene chloride, or alternatively with acetic anhydride and dimethylsulfoxide.

The desired Formula XXI compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 are as described above may be prepared from the corresponding Formula IX compounds by treatment with trimethylsilylcyanide in an inert solvent such as an aromatic hydrocarbon (e.g.,benzene, toluene, xylene) in the presence of a catalytic amount of Lewis acid, preferably zinc iodide, at a temperature of about 25 °C to about 140 °C, preferably about 80 °C to about 100 °C, for 1-12 hours , preferably 5 hours. The resulting solution is concentrated to dryness and added directly without further purification to a polar solvent (e.g., methanol, ethanol). A solution of acid (preferably hydrochloric) in a polar aprotic solvent (preferably dioxane) is added to the solution and the mixture is stirred at a temperature from 0 °C to about 100 °C, preferably

room temperature, for 1 to 24 hours, preferably 12 hours, to yield the Formula XXI compounds.

The desired Formula XXII compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 are as described above may be prepared from the corresponding Formula XXI compounds by treatment with a reducing agent such as sodium borohydride or sodium cyanoborohydride in a reaction inert solvent such as methanol or ethanol, preferably ethanol, at a temperature of about 0 °C to about 100 °C (preferably reflux temperature) for 0.1 to 5 hours (preferably 0.75 hour) to provide the desired Formula XXII compounds.

Alternatively, the desired Formula XXII compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 are as described above may be prepared from the corresponding Formula XVII compounds, wherein Q is a leaving group as described above, by treatment with a cyanide salt such as lithium, sodium, potassium or a tetraalkylammonium cyanide in a reaction inert solvent such as dimethylformamide at a temperature between 0 °C to 100 °C for 1 to 12 hours, to provide the Formula XXII compounds.

The desired Formula XXIII compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 are as described above may be prepared from the corresponding Formula XXII compounds by dissolving in concentrated sulfuric acid containing five equivalents of water at a temperature from 0°C to 100°C (preferably room temperature) for 1 to 20 hours. The resulting amide is then dissolved in a polar solvent (preferably methylene chloride) and treated with trimethyloxonium tetrafluoroborate at a temperature from 0°C to 100°C (preferably room temperature) for 1-20 hours (preferably 12 hours). The resulting imino ester is then treated with an aqueous base, preferably, lithium, sodium, or potassium hydroxide, in a polar solvent, preferably dioxane, at a temperature between 0°C and 100°C (preferably room temperature) for between 1 to 20 hours to provide the Formula XXIII Compounds.

The desired Formula XXIV compounds wherein R^1, R^2, R^4, R^5, R^6, R^7, R^8 and R^9 are as described above may be prepared from the corresponding Formula XXIII compounds by treating the acid in a reaction inert solvent (preferably dichloromethane) with the corresponding amine (NHR^8R^9) in the presence of 1-hydroxybenzotriazole hydrate (HOBT) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) at a temperature between 0°C to 100°C (preferably ambient temperature) for 1 to 24 hours (preferably 12 hours).

The desired Formula XXV compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 are as described above and V^2 is a group V or CH_2V where V is as described above may be prepared from the corresponding Formula XXIV compounds when R^8 is methyl and R^9 is methoxy (the 'Weinreb' amide) by treatment with a variety of V^2Met compounds where Met is a metal, preferably magnesium or lithium, to produce the desired Formula XXV compounds.

The desired Formula XXVI compounds wherein R^1, R^2, R^4, R^5, R^6, R^7, R^8 and R^9 (which are within the scope of the present invention) are as described above may be prepared from the corresponding Formula XXIV compounds by reduction with a hydride source, preferably sodium borohydride, in the presence of an acid such as trifluoroacetic acid in a reaction inert solvent (preferably tetrahydrofuran) at a temperature of between 0 °C and 100 °C for 1 to 20 hours (preferably 12 hour). When R^8 and/or R^9 is H, the amine may be acylated using standard amide coupling conditions known to those skilled in the art such as those described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, to produce further Formula XXVI compounds.

An alternative preparation of the desired Formula XXVI compounds wherein R^1, R^2, R^4, R^5, R^6 and R^7 are as described above and R^8 and R^9 are H involves reduction of the corresponding Formula XXII compounds using procedures known to those skilled in the art, such as those described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, for example using borane-tetrahydrofuran complex in a reaction inert solvent. These primary amines may subsequently be converted to amides as described above to produce further compounds within the scope of the present invention.

The desired Formula XXVII compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 and V^2 are as described above and X^1 is OH, F, or H, may be prepared from the corresponding Formula XXV compounds by treatment with a reducing agent such as sodium borohydride in a polar solvent such as methanol or ethanol at a temperature of about 0 °C to about 100 °C for 1 to 10 hours (preferably 1 hour) to produce Formula XXVII compounds wherein X^1 is OH.

Formula XXVII compounds when X^1=N may be prepared from the corresponding alcohol (X^1=OH) which is converted to the mesylate and displaced with sodium azide. The azide is hydrogenated to NH_2. One skilled in the art can convert NH_2 to NR^1H by standard reductive amination conditions using the correspounding

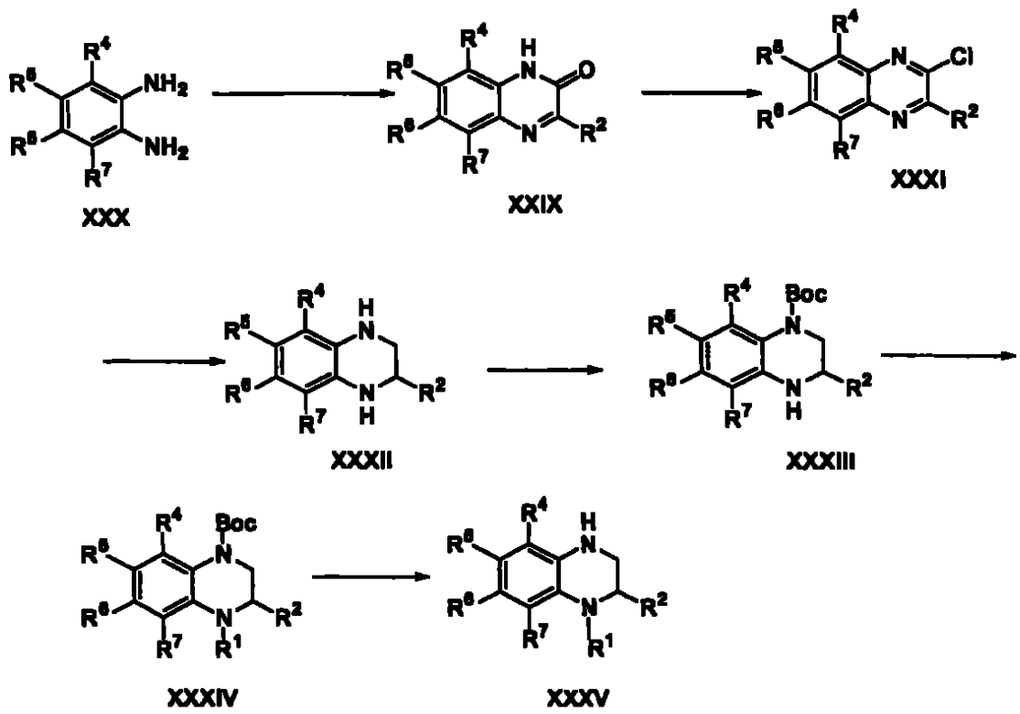
aldehyde and reducing agent, such as sodium borohydride or sodium cyano borohydrite. NR^1H can be converted to NR^1R^2 using the same conditions of reductive amination to produce NR^1R^2.

Moreover, when X^1 is NH_2, the corresponding alcohol (X^1=OH) may be converted to the mesylate, displaced with an azide and reduced with hydrogen to produce one single diastereomer. When X^1 is NHR^1 (R^1=Me), the corresponding primary amine NH_2 may be converted to NHR^1 by treatment with ethyl formate at a temperature between 0 °C to 100 °C between 1-24 hours (preferably 12 hours). The resulting formamide is added directly without further purification to a nonpolar solvent (e.g., benzene, toluene, preferably toluene) and a reducing agent such as borane methyl sulfide complex at a temperature between 0 °C to 100 °C between 1-24 hours (preferably 12 hours) to provide the desired mono methyl amine product. When X^1 is NHR^1, the corresponding primary amine NH_2 may be converted to NHR^1 by standard reductive amination conditions by treatment with an aldehyde R^1 in a polar solvent such as methanol or ethanol in the presence of sodium borohydride or sodium cyanoborohydride at a temperature between 0 °C to 100 °C between 1-24 hours (preferably 12 hours). When X^1 is NR^1R^2, the corresponding secondary amine NHR^1 may be converted to NR^1R^2 by standard reductive as described above. Compound XXV may also be converted to NH_2, NHR^1, and NR^1R^2 by standard reductive amination conditions with the corresponding aldehyde or ketone as described above. This method produces a mixture of amine diastereomers that may be separated by silica gel chromatography.

These may be converted to the corresponding Formula XXVII compounds where X^1 is F by treatment with a fluorinating agent, such as diethylaminosulfur trifluoride (DAST) or [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxyfluor) in a reaction inert solvent such as dichloromethane or 1,2 dichloroethane at a temperature between -78 °C to about 100°C (preferably ambient temperature) for 0.1 to 10 hours (preferably 1 hour). These may be converted to the corresponding Formula XXVII compounds wherein X^1 is H by reduction with a suitable hydride source such as diisobutyl aluminum hydride in a reaction inert solvent such as tetrahydrofuran at a temperature between -78 °C to about 100 °C, preferably about 0 °C, for 0.1 to 10 hours.

The desired Formula XXVIII compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 are as described above and V^2 is a group V or CH_2V where V is as described above may be prepared from the corresponding Formula XXV compounds by treatment with a fluorinating agent, such as diethylaminosulfur trifluoride (DAST) or [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxyfluor) in a reaction inert solvent such as dichloromethane or 1,2-dichloroethane at a temperature between -78 °C to about 100°C (preferably ambient temperature) for 0.1 to 24 hours (preferably 12 hours).

SCHEME 3



SCHEME 3

According to Scheme 3, the desired Formula XXIX compounds wherein J is nitrogen, the optional double bond is absent, and R^2, R^4, R^5, R^6, and R^7 are as described above, may be prepared from the corresponding Formula XXX compounds by reaction with an alpha-ketocarboxylic acid R^2COCO_2H in a protic solvent, such as ethanol or methanol at high temperature. These temperatures can be conveniently and safely achieved using a microwave apparatus familiar to one skilled in the art, such as a Emrys Optimizer (Personal Chemistry, Uppsala, Sweden) or Milestone microwave (Milestone Laboratories, Sorisole, Italy). The resulting reaction mixture is

concentrated to dryness and the Formula XXIX compounds can be usually crystallized or alternatively can be purified by flash chromatography on silica gel.

The desired Formula XXXI compounds wherein R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula XXIX compounds by treatment with a chlorinating agent such as phosphorus (III) chloride, phosphorus (V) oxychloride, thionyl chloride or triphenylphosphine/carbon tetrachloride. Typically Formula XXIX compounds are dissolved in excess phosphorus oxychloride and the mixture is heated to about 100°C, for 12-18h. After cooling excess phosphorus (V) oxychloride is distilled off and the residue is carefully quenched with saturated $NaHCO_3$. The resulting aqueous suspension is extracted with an appropriate organic solvent, preferably methylene chloride.

The desired Formula XXXII compounds wherein R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula XXXI compounds by catalytic hydrogenation in the presence of standard catalysts well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. Typically, the compound is dissolved in an organic solvent, preferably a polar solvent such as acetic acid. Additives such as sodium acetate are usually added to improve the reaction rate. An appropriate catalyst is chosen, such as palladium on carbon. Hydrogenation is carried out at elevated pressures in an appropriate apparatus, preferably for about 6 h. The catalyst is filtered off to yield the Formula XXXII compound, which is typically isolated after chromatography on silica gel.

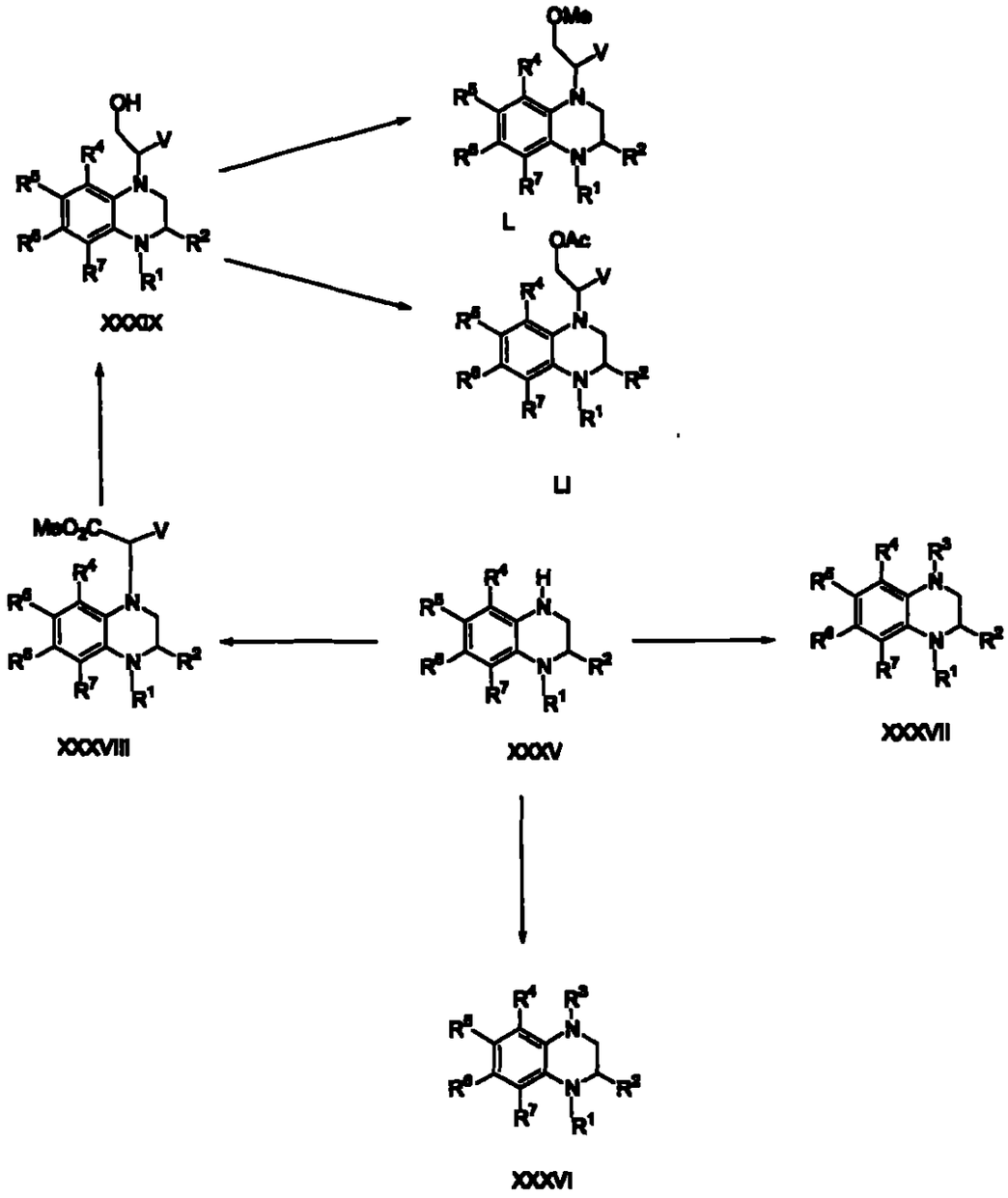
The desired Formula XXXIII compounds wherein R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula XXXII compounds by reaction with boc-anhydride as described in the T. W. Greene and G.M. Wuts, Protective Groups in Organic Synthesis, Wiley Interscience, 1991. Typically, the reaction is carried out in a solvent such as methylene chloride at -78°C to 0°C, typically -40°C. In general, in this procedure, there is a selective functionalization of the less hindered nitrogen in Formula XXXII compounds. The Formula XXXIII compounds can be purified by standard silica gel chromatography, if needed.

The desired Formula XXXIV compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula XXXIII compounds by introducing the acyl, carbamoyl, sulfinyl or sulfonyl group R^1. This may

be achieved by treatment with an appropriate reagent, for example, ethyl chloroformate or isopropyl chloroformate, in a suitable reaction inert solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, typically ambient, for a period of 1 to 24hr. At times, the reaction is carried out in pyridine as a solvent. The product is usually isolated by standard extractive workup and flash chromatography on silica gel.

The desired Formula XXXV compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula XXXIV compound by treatment with an acid as described in the T. W. Greene and G.M. Wuts, Protective Groups in Organic Synthesis, Wiley Interscience, 1991. In a typical procedure, the bis-carbamate is treated with trifluoroacetic acid at ambient temperature for 1-24hr, typically 3hr. Upon completion, the acid is removed by evaporation and the residue is partitioned between an organic solvent, preferably methylene chloride and aqueous sodium hydrogen carbonate. Evaporation of the organic solvent affords the desired Formula XXXV compounds.

SCHEME 4



SCHEME 4

According to Scheme 4, the desired compounds wherein J is nitrogen, the optional double bond is absent, R^1, R^2, R^4, R^5, R^6 and R^7 are as described above and R^3 is as described above wherein the connecting carbon is oxo substituted (depicted as Formula XXXVI compounds) may be prepared from the corresponding Formula

XXXV compounds by reaction with an acid chloride, in a solvent such as methylene chloride or chloroform, optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine or 2,6-di-tert-butyl-4-methylpyridine, at a temperature between 0°C to 60°C, typically ambient, for a period of 1 to 24hr. Upon completion of the reaction, the mixture is washed with aqueous acid and brine to afford the Formula XXXVI compounds after silica gel chromatography. If desired, the acid chloride can be generated *in situ*, from the corresponding carboxylic acid and triphenylphosphine in conjunction with agents such as carbon tetrachloride, hexachloroethane or trichloroacetonitrile. This latter procedure can be carried out with resin bound triphenylphosphine which makes it amenable to automated chemistry. Filtration of the resin followed by evaporation and purification on silica gel yields the required compound of Formula XXXVI.

The desired Formula XXXVII compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above and R^3 is as described above, wherein the group V is attached to the connecting carbon, may be prepared from the corresponding Formula XXXV compounds by alkylation with the appropriate alkyl bromides. These alkylations are typically carried out in a polar solvent such as dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone etc. in the presence of a base (e.g., potassium carbonate, triethylamine, pyridine, 4-dimethylaminopyridine, lutidine) at a temperature between 25°C to 200°C, typically 150°C. Due to the unreactivity of quinoxalines, heating in the microwave at the appropriate temperature is particularly suitable for this procedure. Alkylations can be performed with a variety of alkyl bromides, such as arylmethyl bromides or alpha-substituted arylmethyl bromides. Use of suitable microwave equipment such as the Emrys Optimizer (Personal Chemistry, Uppsala, Sweden) or Milestone microwave (Milestone Laboratories, Sorisole, Italy) facilitates these reactions.

The desired Formula XXXVIII compounds, wherein R^1, R^2, R^4, R^5, R^6, R^7 and V are as described above may be prepared from the corresponding alpha-bromoester $VCHBrCO_2Me$ compounds. These alkylations are typically carried out in a polar solvent such as dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone etc. in the presence of a base (e.g., potassium carbonate, triethylamine, pyridine, 4-dimethylaminopyridine, lutidine) at a temperature between 25°C to 200°C, typically 150°C. Due to the unreactivity of quinoxalines, heating in the microwave at the appropriate temperature is particularly suitable for this procedure. Use of suitable

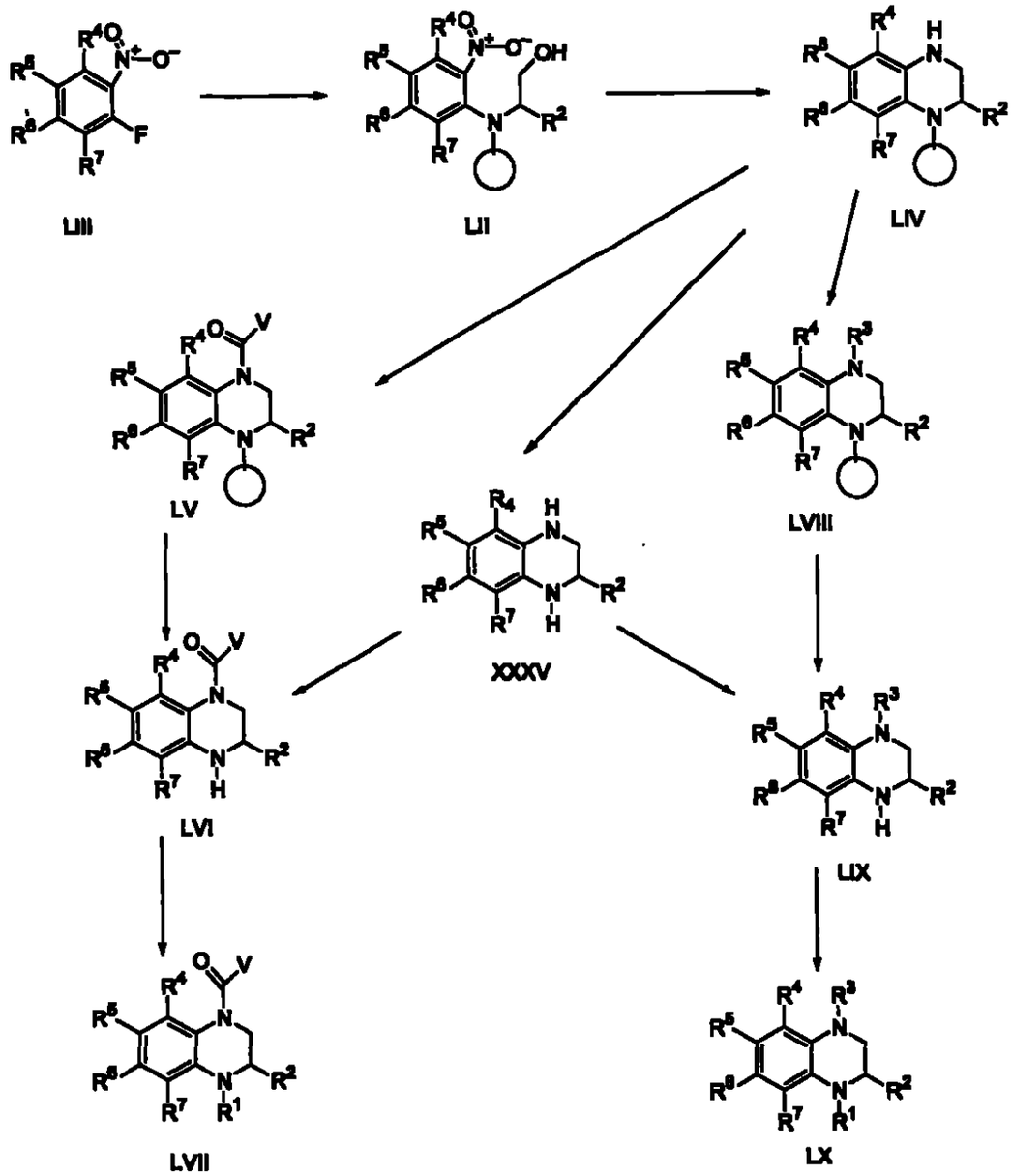
microwave equipment such as the Emrys Optimizer (Personal Chemistry, Uppsala, Sweden) or Milestone microwave (Milestone Laboratories, Sorisole, Italy) facilitates these reactions.

The desired Formula XXXIX compounds, wherein R^1, R^2, R^4, R^5, R^6, R^7 and V are as described above may be prepared from the corresponding Formula XXXVIII compounds by the reduction of the ester functionality using reagents and conditions well known to those skilled in the art. For example, Formula XXXVIII compounds can be treated with lithium aluminum hydride in anhydrous ethereal solvents such as tetrahydrofuran and ether at temperatures ranging between –78°C and 0°C. Typically treating the reaction mixture with sodium sulfate hexahydrate or silica gel/chloroform and removal of the solids by filtration gives a crude product from which Formula XXXIX compounds are typically isolated by silica gel chromatography.

The desired Formula L compounds, wherein R^1, R^2, R^4, R^5, R^6, R^7 and V are as described above may be prepared from the corresponding Formula XXXIX compounds by using an appropriate alkylating agent, such as an alkyl iodide or bromide and a base, such as sodium hydride, in a reaction inert solvent such as tetrahydrofuran or dimethylformamide to obtain the desired Formula L compounds.

The desired Formula LI compounds, wherein R^1, R^2, R^4, R^5, R^6, R^7 and V are as described above and Ac is an acyl group (which are within the scope of the present invention) may be prepared from the corresponding Formula XXXIX compounds by using a suitable acyl chloride and a base such as pyridine, triethylamine or 4-dimethylaminopyridine in an anhydrous solvent such as dichloromethane. Depending on the reactivity of the acyl chloride, one can use the base, such as pyridine, as the solvent. The products can usually be isolated by concentrating the reaction mixture and purifying the product by silica gel chromatography.

SCHEME 5



SCHEME 5

Scheme 5 describes the preparation of further compounds, in which J is nitrogen and the optional double bond is absent (i.e. quinoxalines), using solid phase chemistry similar to that described by V. Krchnak *et.al.*, *Tetrahedron Lett.* 42, 2443-2446 (2001), and which offers several advantages. This chemistry can also be

carried out in the solution phase by substituting the resin with an electron rich arylmethyl group, such as 4-methoxybenzyl or 2,4-dimethoxybenzyl and using it like a protecting group and cleaving under appropriate conditions as described in T.W. Greene and G.M. Wuts, Protective Groups in Organic Synthesis, Wiley Interscience, 1991. In particular, this scheme provides a method for preparation of chiral quinoxalines from chiral aminoalcohols, which are readily prepared from widely available chiral aminoacids using methods and reagents well known to those skilled in the art.

The resin bound Formula LII compounds wherein R^2, R^4, R^5, $R^6$and R^7 are as described above can be prepared from the corresponding aminoalcohol $R^2CH(CH_2OH)NH_2$ which is first bound to a resin by the method described by V. Krchnak *et.al.*, *Tetrahedron Lett. 42*, 2443-2446 (2001). This is then treated with the corresponding Formula LIII compounds typically in a polar solvent such as dimethyl sulfoxide, dimethylformamide, N-methylpyrrolidone or dimethylacetamide which is capable of allowing polystyrene based resin to swell as known to one skilled in the art. The reaction is carried out for 12-36h, and the resin is then washed to isolate the desired resin bound Formula LII compounds.

The desired resin bound Formula LIV compounds, wherein R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding resin bound alcohol of Formula LII compounds by activating the alcohol functionality as familiar to one skilled in the art. This involves the conversion of the alcohol to a sulfonate (such as a methanesulfonate or toluenesulfonate), halide (such as chloride or bromide) or an acetate. Preferably the reaction is carried out by treatment of the resin bound Formula LII compounds with methanesulfonyl chloride in the presence of a base such as pyridine, 4-dimethylaminopyridine or proton sponge in solvents such as dichloromethane or dichloroethane in which case the reaction is typically carried out for 1-5 h. The resulting resin bound sulfonate is washed of all the reagents and the nitro group can be reduced by a variety of reducing agents well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. For example, one can use tin (II) chloride in a polar solvent such as N-methylpyrrolidone or dimethylformamide, which are capable of swelling a polystyrene based resin. The reaction is typically carried out for 1-5h, the reagents are washed away and the resulting primary amine undergoes an intramolecular ring closure to

afford the resin bound Formula LIV compounds. If one uses an activating group other than a methanesulfonate as described above, the reaction times for the ring closure might be longer as known to one skilled in the art.

The resin bound Formula LV compounds wherein R^2, R^4, R^5, R^6, R^7 and V are as described above may be prepared from the corresponding Formula LIV compounds, by reaction with an acid chloride VOCl, in a solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, typically ambient, for a period of 1 to 24hr. The resin bound Formula LV compound is subsequently filtered and repeatedly washed with solvents such as dichloromethane, methanol and water to remove the excess reagents.

The desired Formula LVI compounds wherein R^2, R^4, R^5, R^6, R^7 and V are as described above may be prepared from the corresponding resin bound Formula LV compounds, by treatment with a strong acid well known to those skilled in the art, such as trifluoroacetic acid or hydrofluoric acid, optionally in a reaction-inert solvent such as dichloromethane or dichloroethane. Typically the desired Formula LVI compounds can be isolated by filtration and washing of the resin with an appropriate organic solvent such as dichloromethane, dichloroethane or tetrahydrofuran. If necessary, the Formula LVI compounds can be further purified by silica gel chromatography under standard conditions.

The desired Formula LVII compounds wherein R^1, R^2, R^4, R^5, R^6, R^7 and V are as described above may be prepared from the corresponding Formula LVI compounds by treatment with an appropriate reagent, for example, ethyl chloroformate or isopropyl chloroformate, in a reaction inert solvent such as methylene chloride or chloroform, optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, typically ambient, for a period of 1 to 24hr. At times, the reaction is carried out in pyridine as a solvent. In the particular case where R^1 is a carbamate or urea, the product can be obtained by treating Formula LVI compounds with phosgene in toluene, optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, followed by treatment with, respectively, an alcohol or an amine to afford the desired carbamate or urea of Formula LVII. The

product is usually isolated by standard extractive workup and flash chromatography on silica gel.

The desired resin bound Formula LVIII compounds, wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above and R^3 is as described above, wherein the group V is attached to the connecting carbon, may be prepared from the corresponding resin bound Formula LIV compounds by alkylation with the appropriate alkyl bromides or iodides. These alkylations are typically carried out in a polar solvent such as dimethylformamide, dimethyl sulfoxide or N-methylpyrrolidone in the presence of a base (triethylamine, pyridine, 4-dimethylaminopyridine, lutidine). The solvents used in this reaction are capable of allowing the polystyrene resin to swell as familiar to one skilled in the art. These reactions are usually carried out from ambient temperatures to about 150°C. Due to the unreactivity of quinoxalines, heating in a microwave oven at an appropriate temperature is preferred. Alkylations can be performed with a variety of alkyl bromides such as arylmethyl bromides or alpha-substituted arylmethyl bromides. The alkylation reactions typically proceed in better yield if the bromides are substituted with an alpha electron-withdrawing group (such as in the preparation of the Formula XXXVIII compounds in Scheme 4).

The quinoxaline compounds of Formula LIX wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding resin bound Formula LVIII compounds, by treatment with strong acids well known to those skilled in the art, such as trifluoroacetic acid or hydrofluoric acid, with or without additional solvents (such as dichloromethane or dichloroethane). Typically, the quinoxaline compounds of Formula LIX, can be isolated by filtration and washing of the resin with an appropriate organic solvent such as dichloromethane, dichloroethane or tetrahydrofuran. Evaporation of the solvent usually affords clean desired Formula LIX compounds. If necessary, the isolated products can be further purified by silica gel chromatography under standard conditions.

The desired Formula LX compounds wherein R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding Formula LIX compound by treatment with an acylating/sulfonating agent solvent, for example ethyl or isopropyl chloroformate in a reaction-inert solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, typically ambient, for a period of 1 to 24hr. At times, the reaction is

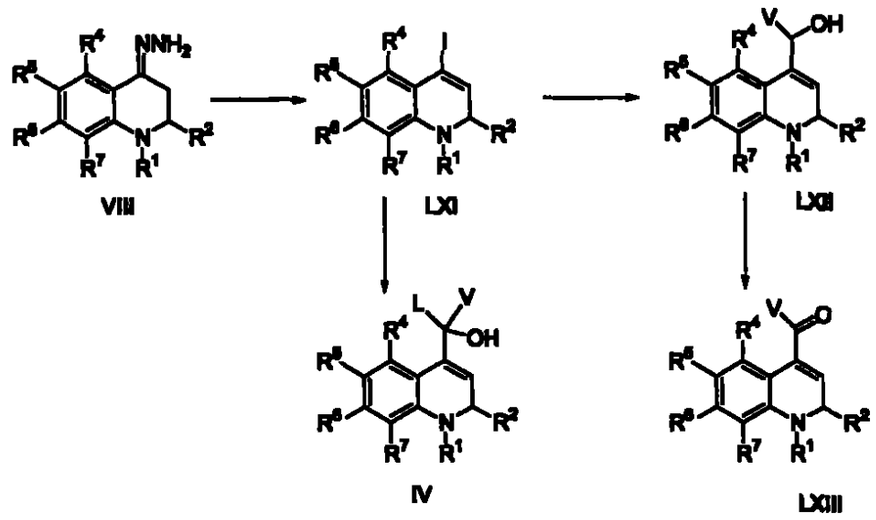
carried out in pyridine as a solvent. In the particular case when R^1 is a carbamate or urea, the product can be obtained by treating Formula LX compound with phosgene in toluene optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, followed by treatment with, respectively, an alcohol or an amine to afford the desired carbamate or urea Formula LX compound. The product is usually isolated by standard extractive workup and flash chromatography on silica gel.

An alternative preparation of the desired Formula LVI compounds wherein R^2, R^4, R^5, R^6, R^7 and V are as described above may be achieved from the corresponding Formula XXXV compounds by reaction with an acylating agent such as acid chloride VOCl, in a solvent such as methylene chloride or chloroform optionally containing a base such as pyridine, diisopropylethylamine, 4-dimethylaminopyridine or 2,6-di-tert-butyl-4-methylpyridine at a temperature between 0°C to 60°C, typically ambient, for a period of 1 to 24hr. Typically under these conditions, when R^2 is other than hydrogen, the less hindered nitrogen atom of the quinoxaline preferentially undergoes acylation to give the desired Formula LVI compounds. The desired compounds of Formula LVII wherein R^1, R^2, R^4, R^5, R^6, R^7 are as described above and R^3 is as described above, wherein the group V is attached to the connecting carbon, may be achieved from the corresponding Formula LVI compounds by alkylation or acylation, using procedures as described above.

An alternative preparation of the desired Formula LIX compounds wherein R^2, R^4, R^5, R^6, R^7 are as described above and R^3 is as described above, wherein the group V is attached to the connecting carbon, may be achieved from the corresponding Formula XXXV compounds, via the compounds of Formula LIX, by alkylation with the appropriate alkyl bromides or iodides. These alkylations are typically carried out in a polar solvent such as dimethylformamide, dimethyl sulfoxide, and N-methylpyrrolidone in the presence of a base (e.g., triethylamine, pyridine, 4-dimethylaminopyridine, lutidine). These reactions are usually carried out from ambient temperatures to about 150°C. Due to the unreactivity of quinoxalines, heating in a microwave oven at an appropriate temperature is preferred. Alkylations can be performed with a variety of alkyl bromides such as arylmethyl bromides, alpha-substituted arylmethyl bromides. Typically under these conditions, when R^2 is other than hydrogen, the less hindered nitrogen atom of the quinoxaline preferentially undergoes alkylation to give the desired Formula LIX compounds.

The desired Formula XXXV compounds wherein R^2, R^4, R^5, R^6, and R^7 are as described above may be prepared from the corresponding resin bound Formula LIV compounds by treatment with strong acids well known to those skilled in the art, such as trifluoroacetic acid or hydrofluoric acid, optionally in a reaction inert solvent such as dichloromethane or dichloroethane.

SCHEME 6



SCHEME 6

According to reaction Scheme 6, the desired compounds wherein J is carbon, the optional double bond is present, R^3 is a group COV and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above (depicted as Formula LXIII compounds) can be prepared from the corresponding Formula LXII compounds by oxidation of the alcohol. This may be achieved by a wide variety of methods well known to those skilled in the art, for example as described in L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. For example the Formula LXII compounds can be treated with activated manganese (IV) oxide in a suitable reaction inert solvent such as tetrahydrofuran, diethyl ether or dichloromethane at a temperature between 0°C to 25°C, typically ambient, to provide the desired product of Formula LXIII.

The desired Formula LXII compounds wherein V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above can be prepared as a mixture of diastereoisomers from the corresponding Formula LXI compounds by treatment with a suitable transmetallating

agent such as an alkyllithium compound, such as n-butyllithium or s-butyllithium, or an alkylmagnesium halide such as isopropylmagnesium chloride in a suitable reaction inert solvent such as tetrahydrofuran or diethyl ether at a temperature between -120°C to 0°C, typically -78°C, to provide a vinyllithium species which is then reacted with the appropriate aldehyde of formula VCHO at a temperature between -120°C to 0°C, typically -78°C to -23°C, to provide the desired product of Formula LXII. In some cases, it is convenient to add the transmetallation agent to a mixture of the aldehyde and the iodide.

The desired Formula LXI compounds wherein R^1, R^2, R^4, R^5, R^6, and R^7 are as described above can be prepared from the corresponding Formula VIII compounds (prepared as described in Scheme I) using the general procedure described by D.H.R. Barton et al. (Tetrahedron Letters 1983 24, 1605) in which the hydrazone is reacted with iodine in the presence of a suitable hindered base such as 1,1,3,3-tetramethylguanidine in a suitable reaction inert solvent such as tetrahydrofuran at a temperature between 25°C to 100°C, typically 25°C to 85°C, removing the solvent in the course of the reaction, to provide the desired product of Formula LXI.

An alternative preparation of the desired Formula IV compounds wherein L is a (C_1-C_6)alkoxycarbonyl group and V, R^1, R^2, R^4, R^5, R^6, and R^7 are as described above can be accomplished in a manner similar to that described for the preparation of the Formula LXII compounds from the corresponding Formula LXI compounds by treatment with a suitable transmetallating agent such as an alkyllithium compound such as n-butyllithium or s-butyllithium, or an alkylmagnesium halide such as isopropylmagnesium chloride in a suitable reaction inert solvent such as tetrahydrofuran or diethyl ether at a temperature between -120°C to 0°C, typically -78°C, to provide a vinyllithium species, which is then reacted with the appropriate ketone of formula VCOL at a temperature between -120°C to 0°C, typically -78°C to -23°C, to provide the desired product of Formula IV. In some cases, it is convenient to add the transmetallation agent to a mixture of the ketone and the iodide.

As an initial note, in the preparation of compounds, it is noted that some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in intermediates). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation

methods. The need for such protection is readily determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

For example, in the reaction schemes, certain compounds contain primary amines or carboxylic acid functionalities which may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide syntheses (such as N-t-butoxycarbonyl, benzyloxycarbonyl, and 9-fluorenylmethylenoxycarbonyl for amines and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and can typically be removed without chemically altering other functionality in the compound.

Prodrugs of the compounds of the present invention may be prepared according to methods known to those skilled in the art. Exemplary processes are described below.

Prodrugs of this invention where a carboxyl group in a carboxylic acid of the compounds is replaced by an ester may be prepared by combining the carboxylic acid with the appropriate alkyl halide in the presence of a base such as potassium carbonate in an inert solvent such as dimethylformamide at a temperature of about 0 to 100°C for about 1 to about 24 hours. Alternatively the acid is combined with appropriate alcohol as solvent in the presence of a catalytic amount of acid such as concentrated sulfuric acid at a temperature of about 20 to 100°C, preferably at a reflux, for about 1 hour to about 24 hours. Another method is the reaction of the acid with a stoichiometric amount of the alcohol in the presence of a catalytic amount of acid in an inert solvent such as toluene or tetrahydrofuran, with concomitant removal of the water being produced by physical (e.g., Dean-Stark trap) or chemical (e.g., molecular sieves) means.

Prodrugs of this invention where an alcohol function has been derivatized as an ether may be prepared by combining the alcohol with the appropriate alkyl bromide or iodide in the presence of a base such as potassium carbonate in an inert solvent such as dimethylformamide at a temperature of about 0 to 100°C for about 1

to about 24 hours. Alkanoylaminomethyl ethers may be obtained by reaction of the alcohol with a bis-(alkanoylamino)methane in the presence of a catalytic amount of acid in an inert solvent such as tetrahydrofuran, according to a method described in US 4,997,984. Alternatively, these compounds may be prepared by the methods described by Hoffman et al. in J. Org. Chem. 1994, 59, 3530.

Glycosides are prepared by reaction of the alcohol and a carbohydrate in an inert solvent such as toluene in the presence of acid. Typically the water formed in the reaction is removed as it is being formed as described above. An alternate procedure is the reaction of the alcohol with a suitably protected glycosyl halide in the presence of base followed by deprotection.

N-(1-hydroxyalkyl) amides, N-(1-hydroxy-1-(alkoxycarbonyl)methyl) amides may be prepared by the reaction of the parent amide with the appropriate aldehyde under neutral or basic conditions (e.g., sodium ethoxide in ethanol) at temperatures between 25 and 70°C. N-alkoxymethyl or N-1-(alkoxy)alkyl derivatives can be obtained by reaction of the N-unsubstituted compound with the necessary alkyl halide in the presence of a base in an inert solvent.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents (e.g., LDL-cholesterol lowering agents, triglyceride lowering agents) for the treatment of the disease/conditions described herein. For example, they may be used in combination with a HMG-CoA reductase inhibitor, a cholesterol synthesis inhibitor, a cholesterol absorption inhibitor, a MTP/Apo B secretion inhibitor, a PPAR modulator and other cholesterol lowering agents such as a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor, and a bile acid sequestrant. Other pharmaceutical agents would also include the following: a bile acid reuptake inhibitor, an ileal bile acid transporter inhibitor, an ACC inhibitor, an antihypertensive (such as NORVASC®), a selective estrogen receptor modulator, a selective androgen receptor modulator, an antibiotic, an antidiabetic (such as metformin, a PPARγ activator, a sulfonylurea, insulin, an aldose reductase inhibitor (ARI) and a sorbitol dehydrogenase inhibitor (SDI)), and aspirin (acetylsalicylic acid). A slow-release form of niacin is available and is known as Niaspan. Niacin may also be combined with other therapeutic agents such as statins, i.e. lovastatin, which is an HMG-CoA reductase inhibitor and described further below. This combination therapy is known as ADVICOR® (Kos Pharmaceuticals Inc.) In combination therapy

treatment, both the compounds of this invention and the other drug therapies are administered to mammals (e.g., humans, male or female) by conventional methods.

Any HMG-CoA reductase inhibitor may be used in the combination aspect of this invention. The term HMG-CoA reductase inhibitor refers to compounds which inhibit the bioconversion of hydroxymethylglutaryl-coenzyme A to mevalonic acid catalyzed by the enzyme HMG-CoA reductase. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g., Meth. Enzymol. 1981; 71:455-509 and references cited therein). A variety of these compounds are described and referenced below however other HMG-CoA reductase inhibitors will be known to those skilled in the art. U.S. Pat. No. 4,231,938 (the disclosure of which is hereby incorporated by reference) discloses certain compounds isolated after cultivation of a microorganism belonging to the genus *Aspergillus*, such as lovastatin. Also, U.S. Pat. No. 4,444,784 (the disclosure of which is hereby incorporated by reference) discloses synthetic derivatives of the aforementioned compounds, such as simvastatin. Also, U.S. Pat. No. 4,739,073 (the disclosure of which is incorporated by reference) discloses certain substituted indoles, such as fluvastatin. Also, U.S. Pat. No. 4,346,227 (the disclosure of which is incorporated by reference) discloses ML-236B derivatives, such as pravastatin. Also, EP-491226A (the disclosure of which is incorporated by reference) discloses certain pyridyldihydroxyheptanoic acids, such as cerivastatin. In addition, U.S. Pat. No. 5,273,995 (the disclosure of which is incorporated by reference) discloses certain 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones such as atorvastatin and any pharmaceutically acceptable form thereof (i.e. LIPITOR®). Additional HMG-CoA reductase inhibitors include rosuvastatin and pitavastatin.

Any PPAR modulator may be used in the combination aspect of this invention. The term PPAR modulator refers to compounds which modulate peroxisome proliferator activator receptor (PPAR) activity in mammals, particularly humans. Such modulation is readily determined by those skilled in the art according to standard assays known in the literature. It is believed that such compounds, by modulating the PPAR receptor, regulate transcription of key genes involved in lipid and glucose metabolism such as those in fatty acid oxidation and also those involved in high density lipoprotein (HDL) assembly (for example, apolipoprotein AI gene transcription), accordingly reducing whole body fat and increasing HDL cholesterol. By virtue of their activity, these compounds also reduce plasma levels of triglycerides,

VLDL cholesterol, LDL cholesterol and their associated components such as apolipoprotein B in mammals, particularly humans, as well as increasing HDL cholesterol and apolipoprotein AI. Hence, these compounds are useful for the treatment and correction of the various dyslipidemias observed to be associated with the development and incidence of atherosclerosis and cardiovascular disease, including hypoalphalipoproteinemia and hypertriglyceridemia. A variety of these compounds are described and referenced below, however, others will be known to those skilled in the art. International Publication Nos. WO 02/064549 and 02/064130 and U.S. patent application 10/720942, filed November 24, 2003 (the disclosures of which are hereby incorporated by reference) disclose certain compounds which are PPARα activators.

Any MTP/Apo B (microsomal triglyceride transfer protein and or apolipoprotein B) secretion inhibitor may be used in the combination aspect of this invention. The term MTP/Apo B secretion inhibitor refers to compounds which inhibit the secretion of triglycerides, cholesteryl ester, and phospholipids. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g., Wetterau, J. R. 1992; Science 258:999). A variety of these compounds are described and referenced below however other MTP/Apo B secretion inhibitors will be known to those skilled in the art, including imputapride (Bayer) and additional compounds such as those disclosed in WO 96/40640 and WO 98/23593, (two exemplary publications).

For example, the following MTP/Apo B secretion inhibitors are particularly useful:

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4,]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-acetylamino-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

(2-[6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl]-ethyl)-carbamic acid methyl ester;

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide;

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,2-diphenyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide; and

4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-ethoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide.

Any HMG-CoA synthase inhibitor may be used in the combination aspect of this invention. The term HMG-CoA synthase inhibitor refers to compounds which inhibit the biosynthesis of hydroxymethylglutaryl-coenzyme A from acetyl-coenzyme A and acetoacetyl-coenzyme A, catalyzed by the enzyme HMG-CoA synthase. Such inhibition is readily determined by those skilled in the art according to standard assays (Meth Enzymol. 1975; 35:155-160: Meth. Enzymol. 1985; 110:19-26 and references cited therein). A variety of these compounds are described and referenced below, however other HMG-CoA synthase inhibitors will be known to those skilled in the art. U.S. Pat. No. 5,120,729 (the disclosure of which is hereby incorporated by reference) discloses certain beta-lactam derivatives. U.S. Pat. No. 5,064,856 (the disclosure of which is hereby incorporated by reference) discloses certain spiro-lactone derivatives prepared by culturing a microorganism (MF5253). U.S. Pat. No. 4,847,271 (the disclosure of which is hereby incorporated by reference) discloses certain oxetane compounds such as 11-(3-hydroxymethyl-4-oxo-2-oxetayl)-3,5,7-trimethyl-2,4-undeca-dienoic acid derivatives.

Any compound that decreases HMG-CoA reductase gene expression may be used in the combination aspect of this invention. These agents may be HMG-CoA reductase transcription inhibitors that block the transcription of DNA or translation inhibitors that prevent or decrease translation of mRNA coding for HMG-CoA reductase into protein. Such compounds may either affect transcription or translation directly, or may be biotransformed to compounds that have the aforementioned activities by one or more enzymes in the cholesterol biosynthetic cascade or may lead to the accumulation of an isoprene metabolite that has the aforementioned activities. Such compounds may cause this effect by decreasing levels of SREBP (sterol receptor binding protein) by inhibiting the activity of site-1 protease (S1P) or agonizing the oxygenal receptor or SCAP. Such regulation is readily determined by those skilled in the art according to standard assays (Meth. Enzymol. 1985; 110:9-19). Several compounds are described and referenced below, however other inhibitors of HMG-CoA reductase gene expression will be known to those skilled in the art. U.S. Pat. No. 5,041,432 (the disclosure of which is incorporated by reference) discloses certain 15-substituted lanosterol derivatives. Other oxygenated

sterols that suppress synthesis of HMG-CoA reductase are discussed by E.I. Mercer (Prog.Lip. Res. 1993;32:357-416).

Any squalene synthetase inhibitor may be used in the combination aspect of this invention. The term squalene synthetase inhibitor refers to compounds which inhibit the condensation of 2 molecules of farnesylpyrophosphate to form squalene, catalyzed by the enzyme squalene synthetase. Such inhibition is readily determined by those skilled in the art according to standard assays (Meth. Enzymol. 1969; 15: 393-454 and Meth. Enzymol. 1985; 110:359-373 and references contained therein). A variety of these compounds are described in and referenced below however other squalene synthetase inhibitors will be known to those skilled in the art. U.S. Pat. No. 5,026,554 (the disclosure of which is incorporated by reference) discloses fermentation products of the microorganism MF5465 (ATCC 74011) including zaragozic acid. A summary of other patented squalene synthetase inhibitors has been compiled (Curr. Op. Ther. Patents (1993) 861-4).

Any squalene epoxidase inhibitor may be used in the combination aspect of this invention. The term squalene epoxidase inhibitor refers to compounds which inhibit the bioconversion of squalene and molecular oxygen into squalene-2,3-epoxide, catalyzed by the enzyme squalene epoxidase. Such inhibition is readily determined by those skilled in the art according to standard assays (Biochim. Biophys. Acta 1984; 794:466-471). A variety of these compounds are described and referenced below, however other squalene epoxidase inhibitors will be known to those skilled in the art. U.S. Pat. Nos. 5,011,859 and 5,064,864 (the disclosures of which are incorporated by reference) disclose certain fluoro analogs of squalene. EP publication 395,768 A (the disclosure of which is incorporated by reference) discloses certain substituted allylamine derivatives. PCT publication WO 9312069 A (the disclosure of which is hereby incorporated by reference) discloses certain amino alcohol derivatives. U.S. Pat. No. 5,051,534 (the disclosure of which is hereby incorporated by reference) discloses certain cyclopropyloxy-squalene derivatives.

Any squalene cyclase inhibitor may be used as the second component in the combination aspect of this invention. The term squalene cyclase inhibitor refers to compounds which inhibit the bioconversion of squalene-2,3-epoxide to lanosterol, catalyzed by the enzyme squalene cyclase. Such inhibition is readily determined by those skilled in the art according to standard assays (FEBS Lett. 1989;244:347-350.). In addition, the compounds described and referenced below are squalene

cyclase inhibitors, however other squalene cyclase inhibitors will also be known to those skilled in the art. PCT publication WO9410150 (the disclosure of which is hereby incorporated by reference) discloses certain 1,2,3,5,6,7,8,8a-octahydro-5,5,8(beta)-trimethyl-6-isoquinolineamine derivatives, such as N-trifluoroacetyl-1,2,3,5,6,7,8,8a-octahydro-2-allyl-5,5,8(beta)-trimethyl-6(beta)-isoquinolineamine. French patent publication 2697250 (the disclosure of which is hereby incorporated by reference) discloses certain beta, beta-dimethyl-4-piperidine ethanol derivatives such as 1-(1,5,9-trimethyldecyl)-beta,beta-dimethyl-4-piperidineethanol

Any combined squalene epoxidase/squalene cyclase inhibitor may be used as the second component in the combination aspect of this invention. The term combined squalene epoxidase/squalene cyclase inhibitor refers to compounds that inhibit the bioconversion of squalene to lanosterol via a squalene-2,3-epoxide intermediate. In some assays it is not possible to distinguish between squalene epoxidase inhibitors and squalene cyclase inhibitors, however, these assays are recognized by those skilled in the art. Thus, inhibition by combined squalene epoxidase/squalene cyclase inhibitors is readily determined by those skilled in art according to the aforementioned standard assays for squalene cyclase or squalene epoxidase inhibitors. A variety of these compounds are described and referenced below, however other squalene epoxidase/squalene cyclase inhibitors will be known to those skilled in the art. U.S. Pat. Nos. 5,084,461 and 5,278,171 (the disclosures of which are incorporated by reference) disclose certain azadecalin derivatives. EP publication 468,434 (the disclosure of which is incorporated by reference) discloses certain piperidyl ether and thio-ether derivatives such as 2-(1-piperidyl)pentyl isopentyl sulfoxide and 2-(1-piperidyl)ethyl ethyl sulfide. PCT publication WO 9401404 (the disclosure of which is hereby incorporated by reference) discloses certain acyl-piperidines such as 1-(1-oxopentyl-5-phenylthio)-4-(2-hydroxy-1-methyl)-ethyl)piperidine. U.S. Pat. No. 5,102,915 (the disclosure of which is hereby incorporated by reference) discloses certain cyclopropyloxy-squalene derivatives.

The compounds of the present invention can also be administered in combination with naturally occurring compounds that act to lower plasma cholesterol levels. These naturally occurring compounds are commonly called nutracauticals and include, for example, garlic extract and niacin. A slow-release form of niacin is available and is known as Niaspan. Niacin may also be combined with other therapeutic agents such as lovastatin, or another is an HMG-CoA reductase inhibitor.

This combination therapy with lovastatin is known as ADVICOR™ (Kos Pharmaceuticals Inc.).

Any cholesterol absorption inhibitor can be used as an additional in the combination aspect of the present invention. The term cholesterol absorption inhibition refers to the ability of a compound to prevent cholesterol contained within the lumen of the intestine from entering into the intestinal cells and/or passing from within the intestinal cells into the lymph system and/or into the blood stream. Such cholesterol absorption inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Lipid Res. (1993) 34: 377-395). Cholesterol absorption inhibitors are known to those skilled in the art and are described, for example, in PCT WO 94/00480. An example of a recently approved cholesterol absorption inhibitor is ZETIA™ (ezetimibe) (Schering-Plough/Merck).

Any ACAT inhibitor may be used in the combination therapy aspect of the present invention. The term ACAT inhibitor refers to compounds that inhibit the intracellular esterification of dietary cholesterol by the enzyme acyl CoA: cholesterol acyltransferase. Such inhibition may be determined readily by one of skill in the art according to standard assays, such as the method of Heider et al. described in *Journal of Lipid Research.*, 24:1127 (1983). A variety of these compounds are known to those skilled in the art, for example, U.S. Patent No. 5,510,379 discloses certain carboxysulfonates, while WO 96/26948 and WO 96/10559 both disclose urea derivatives having ACAT inhibitory activity. Examples of ACAT inhibitors include compounds such as Avasimibe (Pfizer), CS-505 (Sankyo) and Eflucimibe (Eli Lilly and Pierre Fabre).

A lipase inhibitor may be used in the combination therapy aspect of the present invention. A lipase inhibitor is a compound that inhibits the metabolic cleavage of dietary triglycerides or plasma phospholipids into free fatty acids and the corresponding glycerides (e.g. EL, HL, etc.). Under normal physiological conditions, lipolysis occurs via a two-step process that involves acylation of an activated serine moiety of the lipase enzyme. This leads to the production of a fatty acid-lipase hemiacetal intermediate, which is then cleaved to release a diglyceride. Following further deacylation, the lipase-fatty acid intermediate is cleaved, resulting in free lipase, a glyceride and fatty acid. In the intestine, the resultant free fatty acids and monoglycerides are incorporated into bile acid-phospholipid micelles, which are subsequently absorbed at the level of the brush border of the small

intestine. The micelles eventually enter the peripheral circulation as chylomicrons. Such lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

Pancreatic lipase mediates the metabolic cleavage of fatty acids from triglycerides at the 1- and 3-carbon positions. The primary site of the metabolism of ingested fats is in the duodenum and proximal jejunum by pancreatic lipase, which is usually secreted in vast excess of the amounts necessary for the breakdown of fats in the upper small intestine. Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions. Such pancreatic lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

Gastric lipase is an immunologically distinct lipase that is responsible for approximately 10 to 40% of the digestion of dietary fats. Gastric lipase is secreted in response to mechanical stimulation, ingestion of food, the presence of a fatty meal or by sympathetic agents. Gastric lipolysis of ingested fats is of physiological importance in the provision of fatty acids needed to trigger pancreatic lipase activity in the intestine and is also of importance for fat absorption in a variety of physiological and pathological conditions associated with pancreatic insufficiency. See, for example, C.K. Abrams, et al., *Gastroenterology*, 92,125 (1987). Such gastric lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

A variety of gastric and/or pancreatic lipase inhibitors are known to one of ordinary skill in the art. Preferred lipase inhibitors are those inhibitors that are selected from the group consisting of lipstatin, tetrahydrolipstatin (orlistat), valilactone, esterastin, ebelactone A, and ebelactone B. The compound tetrahydrolipstatin is especially preferred. The lipase inhibitor, N-3-trifluoromethylphenyl-N'-3-chloro-4'-trifluoromethylphanylurea, and the various urea derivatives related thereto, are disclosed in U.S. Patent No. 4,405,644. The lipase inhibitor, esteracin, is disclosed in U.S. Patent Nos. 4,189,438 and 4,242,453. The lipase inhibitor, cyclo-O,O'-[(1,6-hexanediyl)-bis-(iminocarbonyl)]dioxime, and the various bis(iminocarbonyl)dioximes related thereto may be prepared as described in Petersen et al., *Liebig's Annalen*, 562, 205-229 (1949).

A variety of pancreatic lipase inhibitors are described herein below. The pancreatic lipase inhibitors lipstatin, (2S, 3S, 5S, 7Z, 10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecanoic acid lactone, and tetrahydrolipstatin (orlistat), (2S, 3S, 5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, and the variously substituted N-formylleucine derivatives and stereoisomers thereof, are disclosed in U.S. Patent No. 4,598,089. For example, tetrahydrolipstatin is prepared as described in, e.g., U.S. Patent Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874. The pancreatic lipase inhibitor, FL-386, 1-[4-(2-methylpropyl)cyclohexyl]-2-[(phenylsulfonyl)oxy]-ethanone, and the variously substituted sulfonate derivatives related thereto, are disclosed in U.S. Patent No. 4,452,813. The pancreatic lipase inhibitor, WAY-121898, 4-phenoxyphenyl-4-methylpiperidin-1-yl-carboxylate, and the various carbamate esters and pharmaceutically acceptable salts related thereto, are disclosed in U.S. Patent Nos. 5,512,565; 5,391,571 and 5,602,151. The pancreatic lipase inhibitor, valilactone, and a process for the preparation thereof by the microbial cultivation of *Actinomycetes* strain MG147-CF2, are disclosed in Kitahara, et al., *J. Antibiotics*, 40 (11), 1647-1650 (1987). The pancreatic lipase inhibitors, ebelactone A and ebelactone B, and a process for the preparation thereof by the microbial cultivation of *Actinomycetes* strain MG7-G1, are disclosed in Umezawa, et al., *J. Antibiotics*, 33, 1594-1596 (1980). The use of ebelactones A and B in the suppression of monoglyceride formation is disclosed in Japanese Kokai 08-143457, published June 4, 1996.

Other compounds that are marketed for hyperlipidemia, including hypercholesterolemia and which are intended to help prevent or treat atherosclerosis include bile acid sequestrants, such as Welchol®, Colestid®, LoCholest® and Questran®; and fibric acid derivatives, such as Atromid®, Lopid® and Tricor®.

Diabetes can be treated by administering to a patient having diabetes (especially Type II), insulin resistance, impaired glucose tolerance, metabolic syndrome, or the like, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a compound of the present invention in combination with other agents (e.g., insulin) that can be used to treat diabetes. This includes the classes of anti-diabetic agents (and specific agents) described herein.

Any glycogen phosphorylase inhibitor can be used as the second agent in combination with a compound of the present invention. The term glycogen phosphorylase inhibitor refers to compounds that inhibit the bioconversion of glycogen to glucose-1-phosphate which is catalyzed by the enzyme glycogen phosphorylase. Such glycogen phosphorylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Med. Chem. 41 (1998) 2934-2938). A variety of glycogen phosphorylase inhibitors are known to those skilled in the art including those described in WO 96/39384 and WO 96/39385.

Any aldose reductase inhibitor can be used in combination with a compound of the present invention. The term aldose reductase inhibitor refers to compounds that inhibit the bioconversion of glucose to sorbitol, which is catalyzed by the enzyme aldose reductase. Aldose reductase inhibition is readily determined by those skilled in the art according to standard assays (e.g., J. Malone, *Diabetes*, 29:861-864 (1980). "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are known to those skilled in the art.

Any sorbitol dehydrogenase inhibitor can be used in combination with a compound of the present invention. The term sorbitol dehydrogenase inhibitor refers to compounds that inhibit the bioconversion of sorbitol to fructose which is catalyzed by the enzyme sorbitol dehydrogenase. Such sorbitol dehydrogenase inhibitor activity is readily determined by those skilled in the art according to standard assays (e.g., Analyt. Biochem (2000) 280: 329-331). A variety of sorbitol dehydrogenase inhibitors are known, for example, U.S. Patent Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

Any glucosidase inhibitor can be used in combination with a compound of the present invention. A glucosidase inhibitor inhibits the enzymatic hydrolysis of complex carbohydrates by glycoside hydrolases, for example amylase or maltase, into bioavailable simple sugars, for example, glucose. The rapid metabolic action of glucosidases, particularly following the intake of high levels of carbohydrates, results in a state of alimentary hyperglycemia which, in adipose or diabetic subjects, leads to enhanced secretion of insulin, increased fat synthesis and a reduction in fat degradation. Following such hyperglycemias, hypoglycemia frequently occurs, due to the augmented levels of insulin present. Additionally, it is

known chyme remaining in the stomach promotes the production of gastric juice, which initiates or favors the development of gastritis or duodenal ulcers. Accordingly, glucosidase inhibitors are known to have utility in accelerating the passage of carbohydrates through the stomach and inhibiting the absorption of glucose from the intestine. Furthermore, the conversion of carbohydrates into lipids of the fatty tissue and the subsequent incorporation of alimentary fat into fatty tissue deposits is accordingly reduced or delayed, with the concomitant benefit of reducing or preventing the deleterious abnormalities resulting therefrom. Such glucosidase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Biochemistry (1969) 8: 4214).

A generally preferred glucosidase inhibitor includes an amylase inhibitor. An amylase inhibitor is a glucosidase inhibitor that inhibits the enzymatic degradation of starch or glycogen into maltose. Such amylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. (1955) 1: 149). The inhibition of such enzymatic degradation is beneficial in reducing amounts of bioavailable sugars, including glucose and maltose, and the concomitant deleterious conditions resulting therefrom.

A variety of glucosidase inhibitors are known to one of ordinary skill in the art and examples are provided below. Preferred glucosidase inhibitors are those inhibitors that are selected from the group consisting of acarbose, adiposine, voglibose, miglitol, emiglitate, camiglibose, tendamistate, trestatin, pradimicin-Q and salbostatin. The glucosidase inhibitor, acarbose, and the various amino sugar derivatives related thereto are disclosed in U.S. Patent Nos. 4,062,950 and 4,174,439 respectively. The glucosidase inhibitor, adiposine, is disclosed in U.S. Patent No. 4,254,256. The glucosidase inhibitor, voglibose, 3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-*C*-(hydroxymethyl)-*D*-epi-inositol, and the various N-substituted pseudo-aminosugars related thereto, are disclosed in U.S. Patent No. 4,701,559. The glucosidase inhibitor, miglitol, (2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)-3,4,5-piperidinetriol, and the various 3,4,5-trihydroxypiperidines related thereto, are disclosed in U.S. Patent No. 4,639,436. The glucosidase inhibitor, emiglitate, ethyl *p*-[2-[(2*R*,3*R*,4*R*,5*S*)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]ethoxy]-benzoate, the various derivatives related thereto and pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Patent No. 5,192,772. The glucosidase inhibitor, MDL-25637, 2,6-dideoxy-7-*O*-β-

D-glucopyrano-syl-2,6-imino-D-glycero-L-gluco-heptitol, the various homodisaccharides related thereto and the pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Patent No. 4,634,765. The glucosidase inhibitor, camiglibose, methyl 6-deoxy-6-[(2*R*,3*R*,4*R*,5*S*)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]-α-D-glucopyranoside sesquihydrate, the deoxynojirimycin derivatives related thereto, the various pharmaceutically acceptable salts thereof and synthetic methods for the preparation thereof, are disclosed in U.S. Patent Nos. 5,157,116 and 5,504,078. The glycosidase inhibitor, salbostatin and the various pseudosaccharides related thereto, are disclosed in U.S. Patent No. 5,091,524.

A variety of amylase inhibitors are known to one of ordinary skill in the art. The amylase inhibitor, tendamistat and the various cyclic peptides related thereto, are disclosed in U.S. Patent No. 4,451,455. The amylase inhibitor AI-3688 and the various cyclic polypeptides related thereto are disclosed in U.S. Patent No. 4,623,714. The amylase inhibitor, trestatin, consisting of a mixture of trestatin A, trestatin B and trestatin C and the various trehalose-containing aminosugars related thereto are disclosed in U.S. Patent No. 4,273,765.

Additional anti-diabetic compounds, which can be used as the second agent in combination with a compound of the present invention, includes, for example, the following: biguanides (e.g., metformin), insulin secretagogues (e.g., sulfonylureas and glinides), glitazones, non-glitazone PPARγ agonists, PPARβ agonists, inhibitors of DPP-IV, inhibitors of PDE5, inhibitors of GSK-3, glucagon antagonists, inhibitors of f-1,6-BPase(Metabasis/Sankyo), GLP-1/analogs (AC 2993, also known as exendin-4), insulin and insulin mimetics (Merck natural products). Other examples would include PKC-β inhibitors and AGE breakers.

The compounds of the present invention can be used in combination with other anti-obesity agents. Any anti-obesity agent can be used as the second agent in such combinations and examples are provided herein. Such anti-obesity activity is readily determined by those skilled in the art according to standard assays known in the art.

Suitable anti-obesity agents include phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, β_3 adrenergic receptor agonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (e.g.,

sibutramine), sympathomimetic agents, serotoninergic agents, cannabinoid receptor antagonists (e.g., rimonabant (SR-141,716A)), dopamine agonists (e.g., bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (e.g., tetrahydrolipstatin, i.e. orlistat), bombesin agonists, anorectic agents (e.g., a bombesin agonist), Neuropeptide-Y antagonists, thyroxine, thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (e.g., Axokine™), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists, and the like.

Any thyromimetic can be used as the second agent in combination with a compound of the present invention. Such thyromimetic activity is readily determined by those skilled in the art according to standard assays (e.g., Atherosclerosis (1996) 126: 53-63). A variety of thyromimetic agents are known to those skilled in the art, for example those disclosed in U.S. Patent Nos. 4,766,121; 4,826,876; 4,910,305; 5,061,798; 5,284,971; 5,401,772; 5,654,468; and 5,569,674. Other antiobesity agents include sibutramine which can be prepared as described in U.S. Patent No. 4,929,629. and bromocriptine which can be prepared as described in U.S. Patent Nos. 3,752,814 and 3,752,888.

The compounds of the present invention can also be used in combination with other antihypertensive agents. Any anti-hypertensive agent can be used as the second agent in such combinations and examples are provided herein. Such antihypertensive activity is readily determined by those skilled in the art according to standard assays (e.g., blood pressure measurements).

Examples of presently marketed products containing antihypertensive agents include calcium channel blockers, such as Cardizem®, Adalat®, Calan®, Cardene®, Covera®, Dilacor®, DynaCirc®, Procardia XL®, Sular®, Tiazac®, Vascor®, Verelan®, Isoptin®, Nimotop®, Norvasc®, and Plendil®; angiotensin converting enzyme (ACE) inhibitors, such as Accupril®, Altace®, Captopril®, Lotensin®, Mavik®, Monopril®, Prinivil®, Univasc®, Vasotec® and Zestril®.

Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated.

The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study has estimated that there will be 4.5 million hip fractures worldwide in 2050.

Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

Those skilled in the art will recognize that anti-resorptive agents (for example progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen, estrogen/progestin combinations, Premarin®, estrone, estriol or 17α- or 17β-ethynyl estradiol) may be used in conjunction with the compounds of the present invention.

Exemplary progestins are available from commercial sources and include: algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate, chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, ethynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogesterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestrone, and tigestol.

Preferred progestins are medroxyprogestrone, norethindrone and norethynodrel.

Exemplary bone resorption inhibiting polyphosphonates include polyphosphonates of the type disclosed in U.S. Patent 3,683,080, the disclosure of

which is incorporated herein by reference. Preferred polyphosphonates are geminal diphosphonates (also referred to as bis-phosphonates). Tiludronate disodium is an especially preferred polyphosphonate. Ibandronic acid is an especially preferred polyphosphonate. Alendronate and resindronate are especially preferred polyphosphonates. Zoledronic acid is an especially preferred polyphosphonate. Other preferred polyphosphonates are 6-amino-1-hydroxy-hexylidene-bisphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt. Hydrolyzable esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1,1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1,1-diphosphonic acid, ethane-2-amino-1,1-diphosphonic acid, propane-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-N,N-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-3,3-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid,N,N-dimethylamino methane diphosphonic acid, N(2-hydroxyethyl) amino methane diphosphonic acid, butane-4-amino-1-hydroxy-1,1-diphosphonic acid, pentane-5-amino-1-hydroxy-1,1-diphosphonic acid, hexane-6-amino-1-hydroxy-1,1-diphosphonic acid and pharmaceutically acceptable esters and salts thereof.

In particular, the compounds of this invention may be combined with a mammalian estrogen agonist/antagonist. Any estrogen agonist/antagonist may be used in the combination aspect of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit bone turnover and/or prevent bone loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art of standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods, and Eriksen E.F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S.J. et al., The Use of Dual-Energy X-Ray Absorptiometry in Animals, Inv. Radiol., 1996,

31(1):50-62; Wahner H.W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described and referenced below.

Another preferred estrogen agonist/antagonist is 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid, which is disclosed in Willson et al., Endocrinology, 1997, 138, 3901-3911.

Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine,2-(-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)) and related compounds which are disclosed in U.S. patent 4,536,516, the disclosure of which is incorporated herein by reference.

Another related compound is 4-hydroxy tamoxifen, which is disclosed in U.S. patent 4,623,660, the disclosure of which is incorporated herein by reference.

A preferred estrogen agonist/antagonist is raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)ethoxy)phenyl)-hydrochloride) which is disclosed in U.S. patent 4,418,068, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is toremifene: (ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. patent 4,996,225, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is centchroman: 1-(2-((4-(-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-pyrrolidine, which is disclosed in U.S. patent 3,822,287, the disclosure of which is incorporated herein by reference. Also preferred is levormeloxifene.

Another preferred estrogen agonist/antagonist is idoxifene: (E)-1-(2-(4-(1-(4-Iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrrolidinone, which is disclosed in U.S. patent 4,839,155, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]- benzo[b]thiophen-6-ol which is disclosed in U.S. Patent No. 5,488,058, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol, which is disclosed in U.S. patent 5,484,795, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT publication no. WO 95/10513 assigned to Pfizer Inc.

Other preferred estrogen agonist/antagonists include the compounds, TSE-424 (Wyeth-Ayerst Laboratories) and arzoxifene.

Other preferred estrogen agonist/antagonists include compounds as described in commonly assigned U.S. patent 5,552,412, the disclosure of which is incorporated herein by reference. Especially preferred compounds described therein are:

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol (also known as lasofoxifene);

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; and

1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

Other estrogen agonist/antagonists are described in U.S. patent 4,133,814 (the disclosure of which is incorporated herein by reference). U.S. patent 4,133,814 discloses derivatives of 2-phenyl-3-aroyl-benzothiophene and 2-phenyl-3-aroylbenzothiophene-1-oxide.

Other anti-osteoporosis agents, which can be used as the second agent in combination with a compound of the present invention, include, for example, the following: parathyroid hormone (PTH) (a bone anabolic agent); parathyroid hormone (PTH) secretagogues (see, e.g., U.S. Patent No. 6,132,774), particularly calcium receptor antagonists; calcitonin; and vitamin D and vitamin D analogs.

Any selective androgen receptor modulator (SARM) can be used in combination with a compound of the present invention. A selective androgen receptor modulator (SARM) is a compound that possesses androgenic activity and which exerts tissue-selective effects. SARM compounds can function as androgen receptor agonists, partial agonists, partial antagonists or antagonists. Examples of suitable SARMs include compounds such as cyproterone acetate, chlormadinone, flutamide, hydroxyflutamide, bicalutamide, nilutamide, spironolactone, 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g] quinoline derivatives, 1,2-dihydropyridino [5,6-g]quinoline derivatives and piperidino[3,2-g]quinolinone derivatives.

Cyproterone, also known as (1b,2b)-6-chloro-1,2-dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione is disclosed in U.S. Patent 3,234,093. Chlormadinone, also known as 17-(acetyloxy)-6-chloropregna-4,6-diene-3,20-dione, in its acetate form, acts as an anti-androgen and is disclosed in U.S. Patent 3,485,852. Nilutamide, also known as 5,5-dimethyl-3-[4-nito-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione and by the trade name Nilandron® is disclosed in U.S. Patent 4,097,578. Flutamide, also known as 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl] propanamide and the trade name Eulexin® is disclosed in U.S. Patent 3,847,988. Bicalutamide, also known as 4'-cyano-a',a',a'-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide and the trade name Casodex® is disclosed in EP-100172. The enantiomers of biclutamide are discussed by Tucker and Chesterton, *J. Med. Chem.* 1988, 31, 885-887. Hydroxyflutamide, a known androgen receptor antagonist in most tissues, has been suggested to function as a SARM for effects on IL-6 production by osteoblasts as disclosed in Hofbauer et al. *J. Bone Miner.* Res. 1999, 14, 1330-1337. Additional SARMs have been disclosed in U.S. Patent 6,017,924; WO 01/16108, WO 01/16133, WO 01/16139, WO 02/00617, WO 02/16310, U.S. Patent Application Publication No. US 2002/0099096, U.S. Patent Application Publication No. US 2003/0022868, WO 03/011302 and WO 03/011824. All of the above refences are hereby incorporated by reference herein.

The starting materials and reagents for the above described compounds, are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, many of the compounds used herein, are related to, or are derived from compounds in which there is a large scientific interest and commercial need, and accordingly many such compounds are commercially available or are reported in the literature or are easily prepared from

other commonly available substances by methods which are reported in the literature.

Some of the compounds of this invention or intermediates in their synthesis have asymmetric carbon atoms and therefore are enantiomers or diastereomers. Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known per se, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by, for example, chiral HPLC methods or converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, an enantiomeric mixture of the compounds or an intermediate in their synthesis which contain an acidic or basic moiety may be separated into their corresponding pure enantiomers by forming a diastereomic salt with an optically pure chiral base or acid (e.g., 1-phenyl-ethyl amine or tartaric acid) and separating the diasteromers by fractional crystallization followed by neutralization to break the salt, thus providing the corresponding pure enantiomers. All such isomers, including diastereomers, enantiomers and mixtures thereof are considered as part of this invention for all of the compounds of the present invention, including the compounds of the present invention. Also, some of the compounds of this invention are atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

More specifically, the compounds of this invention may be obtained in enantiomerically enriched form by resolving the racemate of the final compound or an intermediate in its synthesis, employing chromatography (preferably high pressure liquid chromatography [HPLC]) on an asymmetric resin (preferably Chiralcel™ AD or OD (obtained from Chiral Technologies, Exton, Pennsylvania)) with a mobile phase consisting of a hydrocarbon (preferably heptane or hexane) containing between 0 and 50% isopropanol (preferably between 2 and 20 %) and between 0 and 5% of an alkyl amine (preferably 0.1% of diethylamine). Concentration of the product containing fractions affords the desired materials.

Some of the compounds of this invention are acidic and they form a salt with a pharmaceutically acceptable cation. Some of the compounds of this invention are basic and they form a salt with a pharmaceutically acceptable anion. All such salts are within the scope of this invention and they can be prepared by conventional

methods such as combining the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate. The compounds can be obtained in crystalline form by dissolution in an appropriate solvent(s) such as ethanol, hexanes or water/ethanol mixtures.

In addition, when the compounds of this invention form hydrates or solvates they are also within the scope of the invention.

The compounds of this invention, their prodrugs and the salts of such compounds and prodrugs are all adapted to therapeutic use as agents that inhibit cholesterol ester transfer protein activity in mammals, particularly humans. Thus, the compounds of this invention elevate plasma HDL cholesterol, its associated components, and the functions performed by them in mammals, particularly humans. By virtue of their activity, these agents also reduce plasma levels of triglycerides, VLDL cholesterol, Apo-B, LDL cholesterol and their associated components in mammals, particularly humans. Moreover, these compounds are useful in equalizing LDL cholesterol and HDL cholesterol. Hence, these compounds are useful for the treatment and correction of the various dyslipidemias observed to be associated with the development and incidence of atherosclerosis and cardiovascular disease, including coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, familial-hypercholesterolemia, low HDL and associated components, elevated LDL and associated components, elevated Lp(a), elevated small-dense LDL, elevated VLDL and associated components and post-prandial lipemia.

Further, introduction of a functional CETP gene into an animal lacking CETP (mouse) results in reduced HDL levels (Agellon, L.B., et al: *J. Biol. Chem.* (1991) 266: 10796-10801.) and increased susceptibility to atherosclerosis.(Marotti, K.R., et al: *Nature* (1993) 364: 73-75.). Also, inhibition of CETP activity with an inhibitory antibody raises HDL-cholesterol in hamster (Evans, G.F., et al: *J. of Lipid Research* (1994) 35: 1634-1645.) and rabbit (Whitlock, M.E., et al: *J. Clin. Invest.* (1989) 84: 129-137). Suppression of increased plasma CETP by intravenous injection with antisense oligodeoxynucleotides against CETP mRNA reduced atherosclerosis in

cholesterol-fed rabbits (Sugano, M., et al: *J. of Biol. Chem.* (1998) 273: 5033-5036.) Importantly, human subjects deficient in plasma CETP, due to a genetic mutation possess markedly elevated plasma HDL-cholesterol levels and apolipoprotein A-I, the major apoprotein component of HDL. In addition, most demonstrate markedly decreased plasma LDL cholesterol and apolipoprotein B (the major apolipoprotein component of LDL. (Inazu, A., Brown, M.L., Hesler, C.B., et al.: *N. Engl. J. Med.* (1990) 323: 1234-1238.)

Given the negative correlation between the levels of HDL cholesterol and HDL associated lipoproteins, and the positive correlation between triglycerides, LDL cholesterol, and their associated apolipoproteins in blood with the development of cardiovascular, cerebral vascular and peripheral vascular diseases, the compounds of this invention, their prodrugs and the salts of such compounds and prodrugs, by virtue of their pharmacologic action, are useful for the prevention, arrestment and/or regression of atherosclerosis and its associated disease states. These include cardiovascular disorders (e.g., angina, ischemia, cardiac ischemia and myocardial infarction), complications due to cardiovascular disease therapies (e.g., reperfusion injury and angioplastic restenosis), hypertension, elevated cardiovascular risk associated with hypertension, stroke, atherosclerosis associated with organ transplantation, cerebrovascular disease, cognitive dysfunction (including, but not limited to, dementia secondary to atherosclerosis, transient cerebral ischemic attacks, neurodegeneration, neuronal deficient, and delayed onset or procession of Alzheimer's disease), elevated levels of oxidative stress, elevated levels of C-Reactive Protein, Metabolic Syndrome and elevated levels of HbA1C.

Because of the beneficial effects widely associated with elevated HDL levels, an agent which inhibits CETP activity in humans, by virtue of its HDL increasing ability, also provides valuable avenues for therapy in a number of other disease areas as well.

Thus, given the ability of the compounds of this invention, their prodrugs and the salts of such compounds and prodrugs to alter lipoprotein composition via inhibition of cholesterol ester transfer, they are of use in the treatment of vascular complications associated with diabetes, lipoprotein abnormalities associated with diabetes and sexual dysfunction associated with diabetes and vascular disease. Hyperlipidemia is present in most subjects with diabetes mellitus (Howard, B.V. 1987. J. Lipid Res. 28, 613). Even in the presence of normal lipid levels, diabetic

subjects experience a greater risk of cardiovascular disease (Kannel, W.B. and McGee, D.L. 1979. Diabetes Care 2, 120). CETP-mediated cholesteryl ester transfer is known to be abnormally increased in both insulin-dependent (Bagdade, J.D., Subbaiah, P.V. and Ritter, M.C. 1991. Eur. J. Clin. Invest. 21, 161) and non-insulin dependent diabetes (Bagdade. J.D., Ritter, M.C., Lane, J. and Subbaiah. 1993. Atherosclerosis 104, 69). It has been suggested that the abnormal increase in cholesterol transfer results in changes in lipoprotein composition, particularly for VLDL and LDL, that are more atherogenic (Bagdade, J.D., Wagner, J.D., Rudel, L.L., and Clarkson, T.B. 1995. J. Lipid Res. 36, 759). These changes would not necessarily be observed during routine lipid screening. Thus the present invention will be useful in reducing the risk of vascular complications as a result of the diabetic condition.

The described agents are useful in the treatment of obesity and elevated cardiovascular risk associated with obesity. In both humans (Radeau, T., Lau, P., Robb, M., McDonnell, M., Allhaud, G. and McPherson, R., 1995. *Journal of Lipid Research*. 36 (12):2552-61) and nonhuman primates (Quinet, E., Tall, A., Ramakrishnan, R. and Rudel, L., 1991. *Journal of Clinical Investigation*. 87 (5):1559-66) mRNA for CETP is expressed at high levels in adipose tissue. The adipose message increases with fat feeding (Martin, L. J., Connelly, P. W., Nancoo, D., Wood, N., Zhang, Z. J., Maguire, G., Quinet, E., Tall, A. R., Marcel, Y. L. and McPherson, R., 1993. *Journal of Lipid Research*. 34 (3):437-46), and is translated into functional transfer protein and through secretion contributes significantly to plasma CETP levels. In human adipocytes the bulk of cholesterol is provided by plasma LDL and HDL (Fong, B. S., and Angel, A., 1989. *Biochimica et Biophysica Acta*. 1004 (1):53-60). The uptake of HDL cholesteryl ester is dependent in large part on CETP (Benoist, F., Lau, P., McDonnell, M., Doelle, H., Milne, R. and McPherson, R., 1997. *Journal of Biological Chemistry*. 272 (38):23572-7). This ability of CETP to stimulate HDL cholesteryl uptake, coupled with the enhanced binding of HDL to adipocytes in obese subjects (Jimenez, J. G., Fong, B., Julien, P., Despres, J. P., Rotstein, L., and Angel, A., 1989. *International Journal of Obesity*. 13 (5):699-709), suggests a role for CETP, not only in generating the low HDL phenotype for these subjects, but in the development of obesity itself by promoting cholesterol accumulation. Inhibitors of CETP activity that block this process therefore serve as useful adjuvants to dietary therapy in causing weight reduction.

CETP inhibitors are useful in the treatment of inflammation due to Gram-negative sepsis and septic shock. For example, the systemic toxicity of Gram-negative sepsis is in large part due to endotoxin, a lipopolysaccharide (LPS) released from the outer surface of the bacteria, which causes an extensive inflammatory response. Lipopolysaccharide can form complexes with lipoproteins (Ulevitch, R.J., Johnston, A.R., and Weinstein, D.B., 1981. J. Clin. Invest. 67, 827-37). In vitro studies have demonstrated that binding of LPS to HDL substantially reduces the production and release of mediators of inflammation (Ulevitch, R.J., Johnston, A.R., 1978. J. Clin. Invest. 62, 1313-24). In vivo studies show that transgenic mice expressing human apo-AI and elevated HDL levels are protected from septic shock (Levine, D.M., Parker, T.S., Donnelly, T.M., Walsh, A.M., and Rubin, A.L. 1993. Proc. Natl. Acad. Sci. 90, 12040-44). Importantly, administration of reconstituted HDL to humans challenged with endotoxin resulted in a decreased inflammatory response (Pajkrt, D., Doran, J.E., Koster, F., Lerch, P.G., Arnet, B., van der Poll, T., ten Cate, J.W., and van Deventer, S.J.H. 1996. J. Exp. Med. 184, 1601-08). The CETP inhibitors, by virtue of the fact that they raise HDL levels, attenuate the development of inflammation and septic shock. These compounds would also be useful in the treatment of endotoxemia, autoimmune diseases and other systemic disease indications, organ or tissue transplant rejection and cancer.

The utility of the compounds of the invention, their prodrugs and the salts of such compounds and prodrugs as medical agents in the treatment of the above described disease/conditions in mammals (e.g. humans, male or female) is demonstrated by the activity of the compounds of this invention in conventional assays and the *in vivo* assay described below. The *in vivo* assay (with appropriate modifications within the skill in the art) may be used to determine the activity of other lipid or triglyceride controlling agents as well as the compounds of this invention. The combination protocol described below is useful for demonstrating the utility of the combinations of the lipid and triglyceride agents (e.g., the compounds of this invention) described herein. Such assays also provide a means whereby the activities of the compounds of this invention, their prodrugs and the salts of such compounds and prodrugs (or the other agents described herein) can be compared to each other and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

The following protocols can of course be varied by those skilled in the art.

The hyperalphacholesterolemic activity of the compounds can be determined by assessing the effect of these compounds on the action of cholesteryl ester transfer protein by measuring the relative transfer ratio of radiolabeled lipids between lipoprotein fractions, essentially as previously described by Morton in J. Biol. Chem. 256, 11992, 1981 and by Diss in Clin. Chem. 34, 2322, 1988.

CETP *IN VITRO* ASSAY

The following is a brief description of assays of cholesteryl ester transfer in 97% (whole) or diluted human plasma (*in vitro*) and animal plasma (*ex vivo*): CETP activity in the presence or absence of drug is assayed by determining the transfer of ^{3}H-labeled cholesteryl oleate (CO) from exogenous tracer HDL or LDL to the nonHDL or HDL lipoprotein fraction in human plasma, respectively, or from ^{3}H-labeled LDL to the HDL fraction in animal plasma. Labeled human lipoprotein substrates are prepared similarly to the method described by Morton in which the endogenous CETP activity in plasma is employed to transfer ^{3}H-CO from phospholipid liposomes to all the lipoprotein fractions in plasma. ^{3}H-labeled LDL and HDL are subsequently isolated by sequential ultracentrifugation at the density cuts of 1.019-1.063 and 1.10-1.21 g/ml, respectively.

For the 97% or whole plasma activity assay, ^{3}H-labeled HDL is added to plasma at 10-25 nmoles CO/ml and the samples incubated at 37° C for 2.5-3 hrs. Non-HDL lipoproteins are then precipitated by the addition of an equal volume of 20% (wt/vol) polyethylene glycol 8000 (Diss). The samples are centrifuged 750 g x 20 minutes and the radioactivity contained in the HDL-containing supernatant determined by liquid scintillation counting. Introducing varying quantities of the compounds of this invention as a solution in dimethylsulfoxide into human plasma, before addition of the radiolabeled cholesteryl oleate, and comparing the amounts of radiolabel transferred compared to incubations containing no inhibitor compounds allows the cholesteryl ester transfer inhibitory activities to be determined.

When a more sensitive assay is desirable, an in vitro assay using diluted human plasma is utilized. For this assay, ^{3}H-labeled LDL is added to plasma at 50 nmoles CO/ml and the samples incubated at 37° C for 7 hrs. Non-HDL lipoproteins are then precipitated by the addition of potassium phosphate to 100 mM final concentration followed by manganese chloride to 20 mM final concentration. After vortexing, the samples are centrifuged 750 g x 20 minutes and the radioactivity

contained in the HDL-containing supernatant determined by liquid scintillation counting. Introducing varying quantities of the compounds of this invention as a solution in dimethylsulfoxide into diluted human plasma, before addition of the radiolabeled cholesteryl oleate, and comparing the amounts of radiolabel transferred compared to incubations containing no inhibitor compounds allows the cholesteryl ester transfer inhibitory activities to be determined. This assay has been adapted to run in microliter plate format with liquid scintillation counting accomplished using a Wallac plate reader.

CETP IN VIVO ASSAY

Activity of these compounds *in vivo* can be determined by the amount of agent required to be administered, relative to control, to inhibit cholesteryl ester transfer activity by 50% at various time points *ex vivo* or to elevate HDL cholesterol by a given percentage in a CETP-containing animal species. Transgenic mice expressing both human CETP and human apolipoprotein AI (Charles River, Boston, MA) may be used to assess compounds *in vivo*. The compounds to be examined are administered by oral gavage in an emulsion vehicle containing 20% (v:v) olive oil and 80% sodium taurocholate (0.5%). Blood is taken from mice retroorbitally before dosing, if a predose blood sample is desirable. At various times after dosing, ranging from 4h to 24h, the animals are sacrificed, blood obtained by heart puncture, and lipid parameters measured, including total cholesterol, HDL and LDL cholesterol, and triglycerides. CETP activity is determined by a method similar to that described above except that ^{3}H-cholesteryl oleate-containing LDL is used as the donor source as opposed to HDL. The values obtained for lipids and transfer activity are compared to those obtained prior to dosing and/or to those from mice receiving vehicle alone.

PLASMA LIPIDS ASSAY

The activity of these compounds may also be demonstrated by determining the amount of agent required to alter plasma lipid levels, for example HDL cholesterol levels, LDL cholesterol levels, VLDL cholesterol levels or triglycerides, in the plasma of certain mammals, for example marmosets that possess CETP activity and a plasma lipoprotein profile similar to that of humans (Crook et al. Arteriosclerosis 10, 625, 1990). Adult marmosets are assigned to treatment groups so that each group has a similar mean ±SD for total, HDL, and/or LDL plasma

cholesterol concentrations. After group assignment, marmosets are dosed daily with compound as a dietary admix or by intragastric intubation for from one to eight days. Control marmosets receive only the dosing vehicle. Plasma total, LDL VLDL and HDL cholesterol values can be determined at any point during the study by obtaining blood from an antecubital vein and separating plasma lipoproteins into their individual subclasses by density gradient centrifugation, and by measuring cholesterol concentration as previously described (Crook et al. Arteriosclerosis 10, 625, 1990).

IN VIVO ATHEROSCLEROSIS ASSAY

Anti-atherosclerotic effects of the compounds can be determined by the amount of compound required to reduce the lipid deposition in rabbit aorta. Male New Zealand White rabbits are fed a diet containing 0.2% cholesterol and 10% coconut oil for 4 days (meal-fed once per day). Rabbits are bled from the marginal ear vein and total plasma cholesterol values are determined from these samples. The rabbits are then assigned to treatment groups so that each group has a similar mean ±SD for total plasma cholesterol concentration, HDL cholesterol concentration, triglyceride concentration and/or cholesteryl ester transfer protein activity. After group assignment, rabbits are dosed daily with compound given as a dietary admix or on a small piece of gelatin based confection. Control rabbits receive only the dosing vehicle, be it the food or the gelatin confection. The cholesterol/coconut oil diet is continued along with the compound administration throughout the study. Plasma cholesterol values and cholesteryl ester transfer protein activity can be determined at any point during the study by obtaining blood from the marginal ear vein. After 3-5 months, the rabbits are sacrificed and the aortae are removed from the thoracic arch to the branch of the iliac arteries. The aortae are cleaned of adventitia, opened longitudinally and then analyzed unstained or stained with Sudan IV as described by Holman et. al. (Lab. Invest. 1958, 7, 42-47). The percent of the lesioned surface area is quantitated by densitometry using an Optimas Image Analyzing System (Image Processing Systems). Reduced lipid deposition is indicated by a reduction in the percent of lesioned surface area in the compound-receiving group in comparison with the control rabbits.

ANTIOBESITY PROTOCOL

The ability of CETP inhibitors to cause weight loss can be assessed in obese human subjects with body mass index (BMI) ≥ 30 kg/m^2. Doses of inhibitor are

administered sufficient to result in an increase of ≥ 25% in HDL cholesterol levels. BMI and body fat distribution, defined as waist (W) to hip (H) ratio (WHR), are monitored during the course of the 3-6 month studies, and the results for treatment groups compared to those receiving placebo.

IN VIVO SEPSIS ASSAY

In vivo studies show that transgenic mice expressing human apo-AI and elevated HDL levels are protected from septic shock. Thus the ability of CETP inhibitors to protect from septic shock can be demonstrated in transgenic mice expressing both human apo-AI and human CETP transgenes (Levine, D. M., Parker, T.S., Donnelly, T. M., Walsh, A. M. and Rubin, A.L., 1993. Proc. Natl. Acad. Sci. 90, 12040-44). LPS derived from *E. coli* is administered at 30mg/kg by i.p. injection to animals which have been administered a CETP inhibitor at an appropriate dose to result in elevation of HDL. The number of surviving mice is determined at times up to 48h after LPS injection and compared to those mice administered vehicle (minus CETP inhibitor) only.

Administration of the compounds of this invention can be via any method which delivers a compound of this invention systemically and/or locally. These methods include oral routes, parenteral, intraduodenal routes, etc. Generally, the compounds of this invention are administered orally, but parenteral administration (e.g., intravenous, intramuscular, subcutaneous or intramedullary) may be utilized, for example, where oral administration is inappropriate for the target or where the patient is unable to ingest the drug.

In general an amount of a compound of this invention is used that is sufficient to achieve the therapeutic effect desired (e.g., HDL elevation).

In general an effective dosage for the compounds of this invention is about 0.001 to 100 mg/kg/day of the compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug. An especially preferred dosage is about 0.01 to 10 mg/kg/day of the compound, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug.

A dosage of the combination pharmaceutical agents to be used in conjuction with the CETP inhibitors is used that is effective for the indication being treated.

For example, typically an effective dosage for HMG-CoA reductase inhibitors is in the range of 0.01 to 100 mg/kg/day. In general an effect dosage for a PPAR modulator is in the range of 0.01 to 100 mg/kg/day.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle, diluent or carrier as described below. Thus, the compounds of this invention can be administered individually or together in any conventional oral, parenteral, rectal or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or taploca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. A preferred formulation is a solution or suspension in an oil, for example, a vegetable oil, such as olive oil; triglycerides such as those marketed under the name, Miglyol™; or mono- or diglycerides such as those marketed under the name, Capmul™, for example, in a soft gelatin capsule. Antioxidants may be added to prevent long-term degradation as appropriate. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

Pharmaceutical compositions comprising a solid amorphous dispersion of a cholesteryl ester transfer protein (CETP) inhibitor and a concentration-enhancing polymer are described in International Publication No. WO 02/11710, which is hereby incorporated by reference herein. Self-emulsifying formulations of cholesteryl ester transfer protein (CETP) inhibitors are described in International Publication No.

WO 03/000295, which is hereby incorporated by reference herein. Methods for depositing small drug crystals on excipients are set forth in the literature, such as in J. Pharm. Pharmacol. 1987, 39:769-773, which is hereby incorporated by reference herein.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g.,topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

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

Pharmaceutical compositions according to the invention may contain 0.1%-95% of the compound(s) of this invention, preferably 1%-70%. In any event, the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the disease/condition of the subject being treated, e.g., atherosclerosis.

Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, a prodrug thereof or a salt of such compound or prodrug and a second compound as described above. The kit comprises means for containing the separate compositions such as a container, a divided bottle or a divided foil packet. Typically the kit comprises directions for the administration of the separate components. The kit form is

particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of compounds of the present invention can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory

coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of this invention either alone or in combination with each other or other compounds generally will be administered in a convenient formulation. The following formulation examples only are illustrative and are not intended to limit the scope of the present invention.

In the formulations which follow, "active ingredient" means a compound of this invention.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.25-100
Starch, NF	0-650
Starch flowable powder	0-50
Silicone fluid 350 centistokes	0-15

A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Cellulose, microcrystalline	200-650
Silicon dioxide, fumed	10-650
Stearate acid	5-15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.25-100 mg of active ingredients are made up as follows:

Formulation 3: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredients, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° - 60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.25-100 mg of active ingredient per 5 ml dose are made as follows:

Formulation 4: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.25-100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified Water to	5 mL

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Suppositories are prepared as follows:

Formulation 6: Suppositories

Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

An intravenous formulation is prepared as follows:

Formulation 7: Intravenous Solution

Ingredient	Quantity
Active ingredient dissolved in ethanol 1%	20 mg
Intralipid™ emulsion	1,000 mL

The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

Soft gelatin capsules are prepared using the following:

Formulation 8: Soft Gelatin Capsule with Oil Formulation

Ingredient	Quantity (mg/capsule)
Active ingredient	10-500
Olive Oil or Miglyol™ Oil	500-1000

The active ingredient above may also be a combination of agents.

GENERAL EXPERIMENTAL PROCEDURES

The following examples are put forth so as to provide those of ordinary skill in the art with a disclosure and description of how the compounds, compositions, and methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Unless indicated otherwise, percent is percent by weight given the component and the total weight of the composition, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric. Commercial reagents were utilized without further purification. Room or ambient temperature refers to 20-25 °C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration in vacuo means that a rotary evaporator was used. The names for the compounds of the invention were created by the Autonom 2.0 PC-batch version from Beilstein Informationssysteme GmbH (ISBN 3-89536-976-4). The chemical structures depicted may be only exemplary of the general structure or of limited isomers, and not include specific stereochemistry as recited in the chemical name.

NMR spectra were recorded on a Varian Unity 400 (Varian Co., Palo Alto, CA) NMR spectrometer at ambient temperature. Chemical shifts are expressed in parts per million (δ) relative to an external standard (tetramethylsilane). The peak shapes are denoted as follows: s, singlet; d, doublet, t, triplet, q, quartet, m, multiplet with the prefix br indicating a broadened signal. The coupling constant (J) data given have a maximum error of ±0.41Hz due to the digitization of the spectra that are acquired. Mass spectra were obtained by (1) atmospheric pressure chemical ionization (APCI) in alternating positive and negative ion mode using a Fisons Platform II Spectrometer or a Micromass MZD Spectrometer (Micromass, Manchester, UK) or (2) electrospray ionization in alternating positive and negative ion mode using a Micromass MZD Spectrometer (Micromass, Manchester, UK) with a Gilson LC-MS interface (Gilson Instruments, Middleton, WI) or (3) a QP-8000 mass spectrometer (Shimadzu Corporation, Kyoto, Japan) operating in positive or negative single ion monitoring mode, utilizing electrospray ionization or atmospheric pressure chemical ionization. Where the intensity of chlorine- or bromine-containing ions are described, the expected intensity ratio was observed (approximately 3:1 for $^{35}Cl/^{37}Cl$-containing ions

and 1:1 for $^{79}Br/^{81}Br$-containing ions) and the position of only the lower mass ion is given.

Column chromatography was performed with either Baker Silica Gel (40 µm) (J.T. Baker, Phillipsburg, N.J.) or Silica Gel 60 (40-63 µm)(EM Sciences, Gibbstown, N.J.). Flash chromatography was performed using a Flash 12 or Flash 40 column (Biotage, Dyar Corp., Charlottesville, VA). Preparative HPLC purification was performed on a Shimadzu 10A preparative HPLC system (Shimadzu Corporation, Kyoto, Japan) using a model SIL-10A autosampler and model 8A HPLC pumps. Preparative HPLC-MS was performed on an identical system, modified with a QP-8000 mass spectrometer operating in positive or negative single ion monitoring mode, utilizing electrospray ionization or atmospheric pressure chemical ionization. Elution was carried out using water/acetonitrile gradients containing either 0.1% formic acid or ammonium hydroxide as a modifier. In acidic mode, typical columns used include Waters Symmetry C8, 5µm, 19x50mm or 30x50mm, Waters XTerra C18, 5µm, 50x50 (Waters Corp, Milford, MA) or Phenomenex Synergi Max-RP 4µm, 50x50mm (Phenomenex Inc., Torrance, CA). In basic mode, the Phenomenex Synergi Max-RP 4µm, 21.2x50mm or 30x50mm columns (Phenomenex Inc., Torrance, CA) were used.

Optical rotations were determined using a Jasco P-1020 Polarimeter Jasco Inc., Easton, MD)

Dimethylformamide, tetrahydrofuran, toluene and dichloromethane were the anhydrous grade supplied by Aldrich Chemical Company (Milwaukee, WI). Unless otherwise specified, reagents were used as obtained from commercial sources. The terms "concentrated" and "evaporated" refer to removal of solvent at 1-200 mm of mercury pressure on a rotary evaporator with a bath temperature of less than 45°C. The abbreviation "min" stand for "minutes" and "h" or "hr" stand for "hours." The abbreviation "gm" or "g" stand for grams. The abbreviation "µl" or "µL" stand for microliters.

Preparation 1

(*R,S*)-2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Method 1)

To a solution of (*R,S*)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1294gm, 4.09mol, prepared according to the procedure described in WO 0140190) in glacial acetic acid (3882ml) was added a

solution of sodium nitrite (582gm, 8.18mol) in water (1618ml), maintaining a temperature of 20 to 25°C. The solvent was removed under vacuum, the residue dissolved in methylene chloride (2006ml), and the solution was washed with saturated sodium hydrogen carbonate solution. The solvent was removed by distillation at atmospheric pressure and the residue was dissolved in anhydrous ethanol (2888ml) and treated with aqueous sodium hydroxide (62.2gm, 1.55mol). The solvent was removed under vacuum, the residue dissolved in methylene chloride (2000 ml), washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness under vacuum to give the title compound as an oil (1219gm) which was used without further purification in the following procedure.

Preparation 2

(*RS*)-2-Ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R,S*)-2-ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1208gm, 3.81mol) in methylene chloride (4883ml) was added 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), free radical (6.1gm, 0.038mol), and a solution of potassium bromide (45.8gm, 0.381mol) dissolved in water (191ml). A 6 % aqueous sodium hypochlorite solution (7748ml), which had been buffered to pH 8.6 to 9.5 with solid sodium hydrogen carbonate (78gm), was slowly added at 0 to 5°C. The aqueous layer was washed with methylene chloride (1208ml). The combined organic layers were washed with 1.4N hydrochloric acid (1493ml) to which potassium iodide (12.8gm, 0.078moles) had been added, then aqueous sodium thiosulfate (60.8gm, 0.381mol) dissolved in water (1208ml) and finally water (1691ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness under vacuum to give the title compound as a yellow oil (1193gm).

^{1}H-NMR (DMSO-d_6) δ 8.03 (m, 2H), 7.91 (dd, J=9.12, 2.49Hz, 1H), 4.79 (m, 1H), 4.23 (q, J=7.05Hz, 2H), 3.25 (dd, J=17.42, 5.81Hz, 1H), 2.81 (dd, J=17.42, 1.66Hz, 1H), 1.42 (m, 2H), 1.25 (t, J=7.05Hz, 3H), 0.76 (t, J=7.05Hz, 3H).

Preparations 3 and 4

(*R*)-2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3) and (*S*)-2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (4)

(*RS*)-2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester was resolved by chiral chromatography on a 10cm x 25cm column packed with Chiralcel OD (Chiral Technologies Inc., Exton, PA). The racemic ketone (300mg) in methanol (0.84mL) was injected onto the column and eluted with heptane:isopropanol 99:1 at a flow rate of 275mL/min to give the title compounds:

(*R*)-2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (3), retention time 7.82 min, $[\alpha]_D$= −139.81° (c=0.438, chloroform).

(*S*)-2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (4), retention time 8.93 min, $[\alpha]_D$ = +139.7° (c=0.41, chloroform).

Preparation 5

4-Hydrazono-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A mixture of 6,7-dimethoxy-2-methyl-4-oxo-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.00gm, 3.41mmol, prepared according to the procedure described in German Patent DE 2461050), hydrazine hydrate (330µl, 6.80mmol) and ethanol (4.5mL) were heated together in a crimp-topped vial at 150°C for 30 min in a microwave oven (Emrys Optimizer, Personal Chemistry, Uppsala, Sweden). The solvent was removed under vacuum, the residue dissolved in ethanol (4.5mL), hydrazine hydrate (330µl, 6.80mmol) added and the solution was heated as before at 150°C for 30 min. The solvent was evaporated under vacuum to give the title compound as a pale yellow solid.

MS: 308.2 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.39 (s, 1H), 7.03 (brs, 1H), 5.21 (s, 2H), 5.04 (m, 1H), 4.27 (m, 1H), 4.15 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.61 (dd, J=17, 5.81Hz, 1H), 2.53 (dd, J=17, 1.66Hz, 1H), 1.28 (t, J=7.47Hz, 3H), 1.08 (d, J = 6.64Hz, 3H).

Preparation 6

(*R*)-2-Ethyl-4-hydrazono-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A mixture of (*R*)-2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 3, 1.13gm, 3.58mmol), hydrazine hydrate (348µl, 7.16mmol) and ethanol (10mL) were heated in a Dean-Stark apparatus under conditions allowing for slow distillation of the solvent. After 5h approximately 5mL of distillate had been collected. The solution was diluted with an equal volume of

toluene and the solvent was evaporated under vacuum to give a pale green solid which was triturated and rinsed with a little hexanes to give the title compound as a nearly colorless solid (1.07g).

MS: 330.2 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 8.23 (s, 1H), 7.62 (brd, J=8.30Hz, 1H), 7.46 (dd, J=8.30, 1.66Hz, 1H), 5.45 (brs, 2H), 4.82 (m, 1H), 4.28 (m, 1H), 4.24 (m, 1H), 2.64 (m, 2H), 1.38 (m, 2H), 1.31 (t, J=7.47Hz, 3H), 0.84 (t, J = 7.47Hz, 3H).

Preparation 7

4-Diazo-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of 4-hydrazono-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 5, 200mg, 0.65mmol) in diethyl ether (20mL) was added manganese (IV) oxide (400mg, activated, ~85%, Aldrich Chemical Company, Milwaukee, WI). The suspension was stirred at ambient temperature under nitrogen in the dark for 30 min then the solid removed by filtration through Celite® to give the title compound as a fuchsia colored solution which was typically used immediately.

Preparation 8

(*R*)-4-Diazo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*)-2-ethyl-4-hydrazono-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 6, 317mg, 0.962mmol) in diethyl ether (6mL) was added manganese (IV) oxide (1.1g, activated, ~85%, Aldrich Chemical Company, Milwaukee, WI). The suspension was stirred at ambient temperature under nitrogen in the dark for 1.5 h then the solid removed by filtration through Celite®. The filtrate was diluted with toluene (15mL) prior to evaporation to a final volume of approximately 10mL (never to dryness) to give the title compound as a fuchsia colored solution which was typically used immediately.

Preparations 9 and 10

(*R*)-4-Chloro-2-ethyl-4-methoxycarbonecarbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (9) and (*R*)-2-ethyl-4-methoxycarbonecarbonyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (10)

To a solution of (*R*)-4-diazo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 8) prepared from Preparation 6 (317mg, 0.962mmol) as a solution in toluene as described above was added N,N-diisopropylethylamine (335µl, 1.92mmol) followed, dropwise, by methyl chlorooxoacetate (0.962mmol, 88.4µl). The mixture was allowed to stir at room temperature under nitrogen. Gas evolution was observed and the fuchsia color changed to yellow-orange within about 10 min. The solution was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution then water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on silica eluting with a hexanes:ethyl acetate gradient from 19:1 to 4:1 to give the title compounds:

(*R*)-4-Chloro-2-ethyl-4-methoxycarbonecarbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (earlier eluting diastereoisomer, 82mg)

MS: 422.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.72 (d, J=9.13Hz, 1H), 7.58 (m, 1H), 7.54 (s. 1H), 4.57 (m, 1H), 4.27 (m, 1H), 4.25 (m, 1H), 3.95 (s, 3H), 2.85 (dd, J=14.11, 6.64Hz, 1H), 2.77 (dd, J=14.11, 6.92Hz, 1H), 1.61 (m, 1H), 1.52 (m, 1H), 1.30 (t, J=7.47Hz, 3H), 0.87 (t, J = 7.47Hz, 3H).

(*R*)-4-Chloro-2-ethyl-4-methoxycarbonecarbonyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (later eluting diastereoisomer, 73mg)

MS: 422.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.60 (m, 2H), 7.54 (s. 1H), 4.57 (m, 1H), 4.22 (m, 1H), 4.20 (m, 1H), 3.73 (s, 3H), 3.26 (dd, J=13.8, 7.47 Hz, 1H), 2.23 (dd, J=13.8, 6.75 Hz, 1H), 1.65 (m, 1H), 1.53 (m, 1H), 1.27 (t, J=7.47 Hz, 3H), 0.89 (t, J = 7.47 Hz, 3H).

(*R*)-2-Ethyl-4-methoxycarbonecarbonyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester, 133mg

MS: 384.1 $[M-H]^-$ found

^{1}H-NMR ($CDCl_3$) δ 8.27 (s, 1H), 7.71 (brd, J=8.30Hz, 1H), 7.56 (dd, J=8.30, 1.66Hz, 1H), 7.20 (d, J=6.64Hz, 1H), 5.21 (m, 1H), 4.28 (m, 2H), 3.95 (s, 3H), 1.57 (m, 1H), 1.41 (m, 1H), 1.32 (t, J=7.47Hz, 3H), 0.91 (t, J = 7.47Hz, 3H).

Preparation 11

2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Method 2)

To a solution of 2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (0.89gm, 2.83mmol) in methanol (20mL) was added solid sodium borohydride (102mg, 2.8mmol). After 10 min acetone was added to quench the reaction and the mixture was stirred for 2h before evaporating the solvent under vacuum. The residue was dissolved in methylene chloride and the solution was washed with 0.05N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate, diluted with toluene and evaporated to dryness to give the title compound as a mixture of diastereoisomers which were carried forward unseparated.

MS: 318.0 $[M+H]^+$ found

(*trans* isomer- *minor*) ^{1}H-NMR ($CDCl_3$) δ 7.80 (d, J=8.30Hz, 1H), 7.69 (s, 1H), 7.49 (dd, J=8.30, 1.66Hz, 1H), 4.86 (m, 1H), 4.58 (m, 1H), 4.25 (m, 2H), 2.16 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H), 1.32 (t, J=7.47Hz, 3H), 0.90 (t, J=7.47Hz, 3H).

MS: 318.0 $[M+H]^+$ found

(*cis* isomer- major) ^{1}H-NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.58 (d, J=9.13Hz, 1H), 7.50 (dd, J=9.13, 1.66Hz, 1H), 4.55 (m, 1H), 4.41 (m, 1H), 4.24 (m, 2H), 2.52 (ddd, J=13.28, 7.47, 4.98Hz, 1H), 1.87 (m, 1H), 1.60 (m, 1H), 1.48 (m, 1H), 1.30 (t, J=7.47Hz, 3H), 0.85 (t, J=7.47Hz, 3H).

Preparation 12

4-Chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Method 1)

The product from the previous preparation (Preparation 11, 2.83mmol) was dissolved in anhydrous methylene chloride (30mL), cooled to 0°C and triethylamine (1.0mL, 7.17mmol) followed by methanesulfonyl chloride (245µl, 3.16mmol) were added. After 2h, a further aliquot of triethylamine (1.0mL, 7.17mmol) was added, and the mixture stirred at ambient temperature for 15h then washed with water containing 2N hydrochloric acid (10mL). The organic layer was dried over anhydrous sodium sulfate, evaporated to dryness and purified by chromatography on silica eluting with hexanes:acetone 25:1 to give title compound as an unequal mixture of diastereoisomers (590mg) which typically were carried forward unseparated.

Diastereoisomer 1 (Major)

MS: 336.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.69 (d, J=8.29Hz, 1H), 7.60 (s, 1H), 7.63 (d, J=8.29Hz, 1H), 5.12 (dd, J=6.64, 4.98Hz, 1H), 4.60 (m, 1H), 4.27 (m, 2H), 2.60 (ddd, J=14.11, 6.64, 6.64Hz, 1H), 2.13 (ddd, J=14.11, 6.64, 4.98Hz, 1H), 1.64 (m, 1H), 1.54 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.89 (t, J=7.47Hz, 3H).

Diastereoisomer 2 (Minor)

MS: 336.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.82 (s, 1H), 7.68 (d, J=8.30Hz, 1H), 7.51 (dd, J=8.30, 1.66Hz, 1H), 5.08 (dd, J=5.81, 5.81Hz, 1H), 4.55 (m, 1H), 4.25 (m, 2H), 2.71 (ddd, J=14.11, 5.81, 5.81Hz, 1H), 2.18 (ddd, J=14.11, 5.81, 5.81Hz, 1H), 1.74 (m, 1H), 1.60 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.91 (t, J=7.47Hz, 3H).

Preparation 13

(*R, S*)-2-Ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Method 3)

To a solution of (*R*)-2-ethyl-4-oxo-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.1gm, 3.49mmol) in anhydrous tetrahydrofuran at 0°C under nitrogen was added potassium triisobutylborohydride (K-Selectride®, 1M in tetrahydrofuran, 8.0mL, 8mmol). After 1.5h the mixture was allowed to warm to ambient temperature, stirred for 16h then an additional aliquot of K-Selectride® (3.49mL, 3.49mmol) was added. After 1.5h the solvent was removed under vacuum, the residue was dissolved in ethyl acetate (50mL) and this solution was washed with 2N sodium hydroxide solution (20mL) followed by hydrogen peroxide (30%, 15mL), dried over anhydrous magnesium sulfate and concentrated to low volume. The residue was taken up in acetonitrile and evaporated to dryness (x3) to remove residual water to give the title compound (100%), identical to the *cis* isomer of the product described above (Preparation 11).

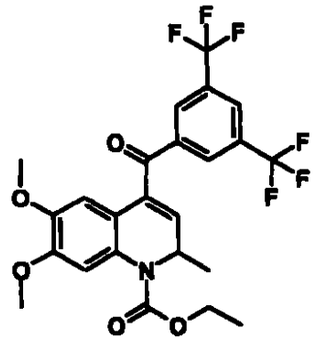
Preparation 14

(*R*)-4-Chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Method 2)

(*R, S*)-2-ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 13, 1.1gm, 3.47mmol) was dissolved in thionyl chloride (20mL) at ambient temperature under nitrogen. After 1h N,N-dimethylformamide (2 drops) was added and the mixture allowed to stir at ambient

temperature for 15h. The solvent was removed under reduced pressure and the residue was chromatographed on silica eluting with ethyl acetate-hexanes 50:1 to give the title compound as a yellow oil (405mg) with a proton NMR spectrum very similar to that obtained for Preparation 12 except that the major and minor components of the mixture were reversed.

Example 1



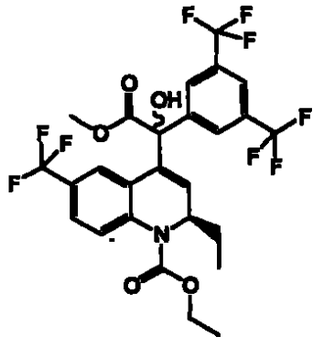
4-(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-2H-quinoline-1-carboxylic acid ethyl ester

A solution of 4-diazo-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 7, 0.65mmol) prepared as a solution in diethyl ether as described above was added to a solution of 3,5-bistrifluoromethylbenzoyl chloride (180mg, 0.65mmol) and N,N-diisopropylethylamine (120µl, 0.65mmol) in diethyl ether (15mL) and allowed to stir at room temperature under nitrogen in the dark for 15h. The solvent was removed under vacuum and the residue was chromatographed on silica eluting with hexanes:ethyl acetate 3:1 to give a partially purified product which was further purified by reverse phase chromatography (linear acetonitrile:water gradient, 55% to 100% acetonitrile, both phases containing 0.1% formic acid) to give the title compound as a lemon yellow solid (90mg).

MS: 518.1 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 8.26 (s, 2H), 8.07 (s, 1H), 7.25 (brs, 1H), 7.04 (s, 1H), 6.32 (d, J=6.64Hz, 1H), 5.31 (m, 1H), 4.33 (m, 1H), 4.23 (m, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 1.33 (t, J=7.47Hz, 3H), 1.20 (d, J=6.64Hz, 3H).

Example 2



(*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

A solution of 3,5-bis(trifluoromethylphenyl)magnesium bromide was prepared by dropwise addition of a solution of 3,5-bistrifluoromethylbromobenzene (0.818mL, 4.74mmol) in anhydrous tetrahydrofuran (0.7mL) to a stirred suspension of magnesium powder (116mg, 4.74mmol) in anhydrous tetrahydrofuran (4.7mL) at 35°C. The mixture was then heated under reflux for 1h to give a dark colored solution. A portion of this solution (1.5mL) was added dropwise to a solution of (*R*)-2-ethyl-4-methoxycarbonecarbonyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 10, 133mg, 0.345mmol) in anhydrous tetrahydrofuran (4mL) at -78°C. After 30 min the mixture was warmed to 0°C and poured into water and extracted with ethyl acetate, adding a few drops of 2N hydrochloric acid to facilitate separation of the layers. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. This procedure was repeated in an exactly similar manner using (*R*)-2-ethyl-4-methoxycarbonecarbonyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 10, 235mg, 0.609mmol) in anhydrous tetrahydrofuran (5mL) and adding the solution of 3,5-bis(trifluoromethylphenyl)magnesium bromide (2mL). The combined crude product was chromatographed on silica eluting with an ethyl acetate-hexanes gradient from 5% to 30% to give the title compound as a mixture of diastereoisomers (463mg) which were carried forward unseperated.

MS: 597.9 [M-H]⁻ found

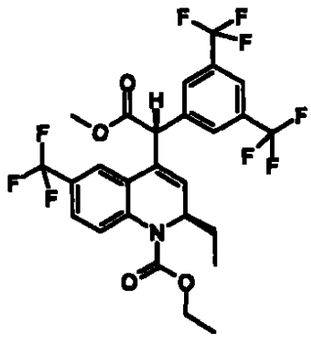
Diastereoisomer 1: ^{1}H-NMR ($CDCl_3$) δ 7.92 (s, 2H), 7.75 (s, 1H), 7.67 (s, 1H), 7.65 (d, J=8.30Hz, 1H), 7.34 (dd, J=8.30, 1.66Hz, 1H), 5.97 (d, J=8.64Hz, 1H), 5.04

(m, 1H), 4.53 (s, 1H), 4.27 (m, 2H), 3.87 (s, 3H), 1.47 (m, 1H), 1.35 (m, 1H), 1.28 (t, J=7.47Hz, 3H), 0.85 (d, J=6.64Hz, 3H).

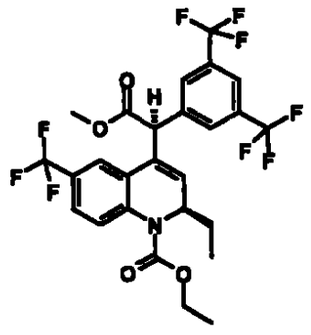
MS: 597.9 [M-H]⁻ found

Diastereoisomer 2: ^{1}H-NMR ($CDCl_3$) δ 8.16 (s, 2H), 7.90 (s, 1H), 7.65 (d, J=8.30, 1H), 7.63 (s, 1H), 7.45 (dd, J=8.30, 1.66Hz, 1H), 5.82 (d, J=6.42Hz, 1H), 4.98 (m, 1H), 4.34 (s, 1H), 4.27 (m, 2H), 3.78 (s, 3H), 1.47 (m, 1H), 1.35 (m, 1H), 1.33 (t, J=7.47Hz, 3H), 0.83 (d, J=7.47Hz, 3H).

Examples 3 and 4



(*R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester



(*R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Example 2, 125mg, 0.208mmol) and 2,6-di-tert-butyl-4-methylpyridine (256mg, 1.248mmol) in chloroform (7mL) was added thionyl chloride (30.4µl, 0.417mmol). After stirring for 18h at ambient temperature the mixture was diluted with methylene chloride, washed with water and dried over anhydrous sodium

sulfate. After removal of the solvent under vacuum the residue was chromatographed on silica eluting with an ethyl acetate-hexanes gradient from 0% to 40% to give 4-[(3,5-bis-trifluoromethyl-phenyl)-chloro-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester as a mixture of diastereoisomers. This material (128mg) was dissolved in a mixture of tetrahydrofuran (2mL) and acetic acid (2mL). Zinc dust (200mg, 3.05mmol) was added followed by 2N hydrochloric acid (1.5mL). The suspension was stirred at ambient temperature for 3h then diluted with methylene chloride and washed with water. The organic layer was dried with anhydrous sodium sulfate and evaporated to dryness under vacuum. The residue was chromatographed on silica eluting with a methylene chloride-hexanes gradient from 60% to 80% to give the title compounds:

Diastereoisomer 1: 44mg

MS: 584.0 $[M+H]^+$ found

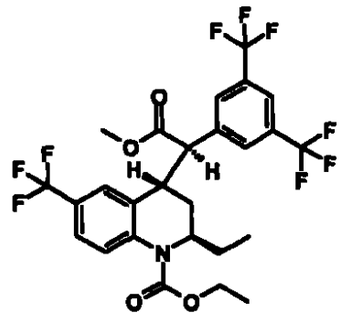
^{1}H-NMR ($CDCl_3$) δ 7.79 (s, 1H), 7.76 (s, 2H), 7.74 (d, J=8.30Hz, 1H), 7.47 (d, J=8.30Hz, 1H), 7.41 (s, 1H), 6.02 (d, J=6.64Hz, 1H), 5.12 (s, 1H), 5.01(m, 1H), 4.26 (m, 2H), 3.62 (s, 3H), 1.53 (m, 1H), 1.40 (m, 1H), 1.30 (t, J=7.47Hz, 3H), 0.87 (d, J=7.47Hz, 3H).

Diastereoisomer 2: 16mg

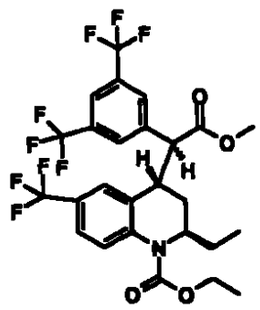
MS: 584.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.88 (s, 2H), 7.87 (s, 1H), 7.77 (d, J=8.30Hz, 1H), 7.49 (d, J=8.30Hz, 1H), 7.33 (s, 1H), 5.96 (d, J=5.81Hz, 1H), 5.07 (s, 1H), 5.00 (m, 1H), 4.29 (m, 2H), 3.74 (s, 3H), 1.47 (m, 1H), 1.36 (m, 1H), 1.34 (t, J=7.47Hz, 3H), 0.84 (d, J=7.47Hz, 3H).

Examples 5 and 6



(*RS, SR, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*RS, SR, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of 4-chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 12, 275mg, 0.82mmol) and 3,5-bis(trifluoromethylphenyl)acetic acid methyl ester (286mg, 1mmol) in anhydrous dimethylformamide (2mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, ~100mg). The mixture was stirred at ambient temperature for 24h then at 50°C for 15h. The mixture was poured into water, acidified by the addition of a little 2N hydrochloric acid and extracted with methylene chloride (x3). The extract was dried over anhydrous sodium sulfate, evaporated to dryness and the residue purified initially by reverse phase chromatography and finally by chromatography on silica eluting with hexanes-ethyl acetate 8:1 to give the title compounds.

(*RS, SR, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (13.8mg, first eluting diastereoisomer)

MS: 586.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.90 (s, 2H), 7.87 (s, 1H), 7.59 (d, J=8.30Hz, 1H), 7.62 (d, J=8.30Hz, 1H), 7.61 (s, 1H), 4.39-4.27 (m, 2H), 4.27-4.18 (m, 1H), 3.78 (d, J=11.61Hz, 1H), 3.59 (m, 1H), 3.48 (s, 3H), 1.76 (ddd, J=14.10, 8.30, 3.30Hz, 1H), 1.61-1.55 (m, 1H),1.57-1.50 (m, 1H), 1.48-1.40 (m, 1H), 1.35 (t, J=7.47Hz, 3H), 0.73 (t, J=7.47Hz, 3H).

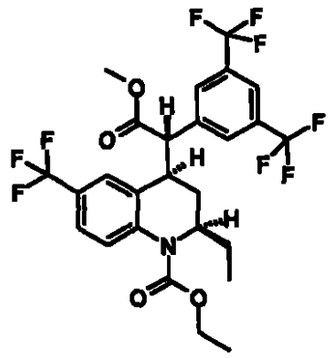
(*RS, SR, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (33.7mg, second eluting diastereoisomer)

MS: 586.0 $[M+H]^+$ found

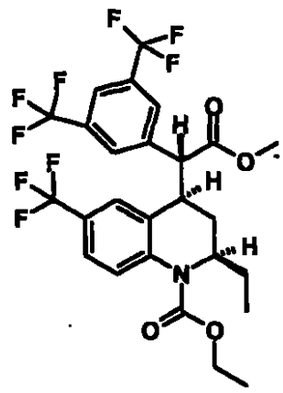
^{1}H-NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.42 (d, J=8.30Hz, 1H), 7.40 (s, 2H), 7.33 (dd, J=8.30, 1.66Hz, 1H), 6.47 (d, J=1.66Hz, 1H), 4.55-4.47 (m, 1H), 4.34 (m, 1H),

4.32 (m,1H), 3.83 (d, J=11.61Hz, 1H), 3.80 (s, 3H), 3.43 (ddd, J=11.61, 4.98, 2.49Hz, 1H), 2.44 (ddd, J=14.11, 8.30, 2.49Hz, 1H), 1.81 (ddd, J=14.10, 8.30, 4.98Hz, 1H), 1.67 (m, 1H),1.51 (m, 1H), 1.33 (t, J=7.47Hz, 3H), 0.85 (t, J=7.47Hz, 3H).

Examples 7 and 8



(*RS, RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(2*S, RS, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A mixture of (*RS, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester and (*RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (prepared by a procedure exactly similar to that described for Examples 3 and 4 with the exception that racemic starting material was used and the mixture of diastereoisomers produced were not separated) (20mg, 0.0342mmol) in ethanol (5mL) containing palladium hydroxide (20% on carbon, 20mg) was hydrogenated in a Parr shaker (Parr Instrument Company, Moline, Illinois) at 40psi for 5h. The catalyst was removed by filtration

through Celite® and the solvent was removed under vacuum. The residue was chromatographed on silica eluting with an ethyl acetate – hexanes gradient from 0% to 10% to give the title compounds.

(*RS, RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (first eluting diastereoisomer, 8mg)

MS: 586.0 $[M+H]^+$ found

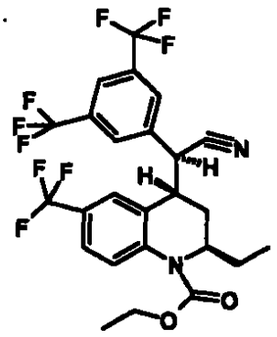
^{1}H-NMR ($CDCl_3$) δ 7.89 (s, 1H), 7.88 (s, 2H), 7.53 (m, 2H), 7.39 (s, 1H), 4.55-4.47 (m, 1H), 4.34-4.24 (m, 2H), 4.24-4.18 (m, 1H), 4.03 (d, J=11.62Hz, 1H), 3.77 (s, 3H), 3.38 (m, 1H), 1.75 (m, 1H), 1.49 (m, 1H), 1.38 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.96 (m, 1H), 0.71 (t, J=7.47Hz, 3H).

(*RS, RS, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (second eluting diastereoisomer, 5mg)

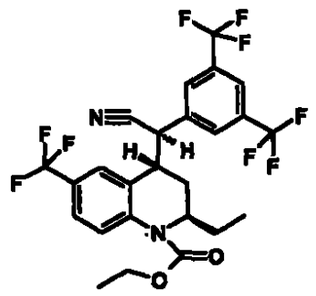
MS: 586.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.93 (s, 2H), 7.84 (s, 1H), 7.53 (d, J=8.29Hz, 1H), 7.43 (dd, J=8.29Hz, 1H), 7.07 (s, 1H), 4.42 (m, 1H), 4.27 (d, J=9.96Hz, 1H), 4.26 (m, 2H), 4.32 (m,1H), 3.76 (s, 3H), 3.28 (m, 1H), 2.36 (m, 1H), 1.65 (m, 1H), 1.62 (m, 1H),1.45 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.84 (t, J=7.47Hz, 3H).

Examples 9 and 10



(*R, S, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

Sodium hydride (60% dispersion in mineral oil, 34mg, 0.85mmol) was added to a solution of 3,5-bis(trifluoromethylphenyl)acetonitrile (212mg, 0.84mmol) in anhydrous dimethylformamide (1.5mL). After stirring under nitrogen for 30 min at ambient temperature a solution of (*R*)-4-chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 14, 188mg, 0.56mmol) in anhydrous dimethylformamide (2mL) was added. The mixture was stirred at ambient temperature for 16h then poured into water (20mL) and extracted with diethyl ether (3x20mL). The extract was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. This material was purified by chromatography on silica eluting initially with ethyl acetate – hexanes (1:19) to obtain one diastereoisomer of the desired compound in an impure form which was further purified by reverse phase chromatography to obtain the title compound Example 9 as a clear oil (69mg). Further elution of the silica column with ethyl acetate – hexanes (1:4) provided the title compound of Example 10 as a yellow oil (54mg).

(*R, S, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

MS: 553 $[M+H]^+$ found

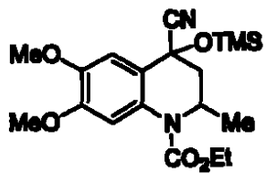
^{1}H-NMR ($CDCl_3$) δ 7.80 (s, 1H), 7.60 (d, J=8.30Hz, 1H), 7.49 (dd, J=8.30, 1.66Hz, 1H), 7.40 (s, 2H), 6.60 (d, J=1.66Hz, 1H), 4.59 (m, 1H), 4.33 (m, 2H), 4.06 (d, J=9.96, 1H), 3.20 (m, 1H), 2.78 (m, 1H), 1.89 (m, 1H), 1.65 (m, 1H), 1.53 (m, 1H), 1.34 (t, J=7.47Hz, 3H), 0.96 (m, 1H), 0.88 (t, J=7.47Hz, 3H).

(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

MS: 553 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.89 (s, 1H), 7.62 (s, 2H), 7.62 (d, J=8.30Hz, 1H), 7.55 (d, J=8.30Hz, 1H), 7.38 (s, 1H), 4.41 (m, 1H), 4.24 (m, 2H), 4.16 (m, 1H), 4.15 (d, J=8.30Hz, 1H), 3.48 (m, 1H), 2.01 (m, 1H), 1.95 (m, 1H), 1.48 (m, 1H), 1.41 (m, 1H), 1.29 (t, J=7.47Hz, 3H), 0.77 (t, J=7.47Hz, 3H).

Preparation 15

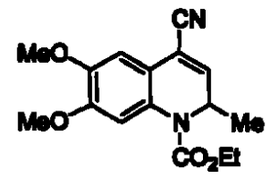


[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-Cyano-6,7-dimethoxy-2-methyl-4-trimethylsilanyloxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*RS*)]-6,7-Dimethoxy-2-methyl-4-oxo-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (8.02gm, 27.3mmol, 1 eq) and zinc iodide (0.43gm, 1.37mmol, 0.05 eq) were added to a dry round bottomed flask equipped with a magnetic stir bar and reflux condenser under a nitrogen atmosphere. Toluene (20mL) was added to the flask followed by trimethylsilyl cyanide (4.40mL, 33.0mmol, 1.2 eq). The reaction was heated to 80 °C. After 5 hr, the reaction mixture was concentrated to dryness to afford the title compounds (10.7gm, 27.2mmol, 100% yield) that were used without further purification.

LCMS (ESI+): 393 (MH+).

Preparation 16



(*RS*) -4-Cyano-6,7-dimethoxy-2-methyl-2*H*-quinoline-1-carboxylic acid ethyl ester

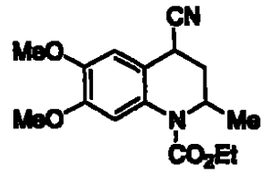
[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-cyano-6,7-dimethoxy-2-methyl-4-trimethylsilanyloxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (10.7gm, 27.37mmol) was placed in a 100mL round bottomed flask and dissolved in ethanol (25 mL). Hydrochloric acid in dioxane (21.0mL of a 4.0 M solution) was added to the mixture. After 12 hr at room temperature, the reaction mixture was concentrated, quenched with a saturated aqueous sodium hydrogen carbonate solution and extracted 3 times with ethyl acetate. The combined organic layers were dried over

anhydrous sodium sulfate, filtered and concentrated. Flash chromatography eluting with 80/20 hexanes/ethyl acetate the title compounds (5.49gm, 18.1mmol, 67% yield).

LCMS (ESI+): 303 (MH+).

^{1}H-NMR ($CDCl_3$): δ 1.13 (d, 3H), 1.33 (t, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.30 (m, 2H), 5.25 (m, 1H), 6.65 (d, 1H), 6.91 (s, 1H), 7.24 (br s, 1H).

Preparations 17 and 18



[(*R*, *S*), ((*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-Cyano-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

(*RS*) -4-Cyano-6,7-dimethoxy-2-methyl-2*H*-quinoline-1-carboxylic acid ethyl ester (4.99gm, 16.5mmol) was placed in a round bottomed flask equipped with a magnetic stir bar, dissolved in 47mL of ethanol, and was combined with sodium borohydride (3.18gm, 84.3mmol, 5.1 eq). After 45 min of heating at reflux, the mixture was concentrated to dryness, quenched with water, and extracted 3 times with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered and concentrated to afford the title compounds (4.91gm, 16.1mmol, 98% yield).

cis isomer:

LCMS (ESI+): 305 (MH+).

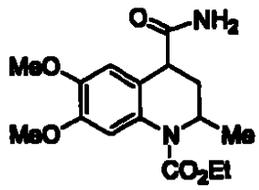
(*R*, *S*) and (*S*, *R*) ^{1}H-NMR ($CDCl_3$): δ 1.23 (d, 3H), 1.29 (t, 3H), 1.78 (m, 1H), 2.65 (m, 1H), 3.74 (m, 1H), 3.86 (s, 3H), 3.90 (s, 3H), 4.22 (m, 2H), 4.61 (m, 1H), 6.92 (s, 1H), 7.10 (s, 1H).

trans isomer:

LCMS (ESI+): 305 (MH+).

(*R*, *R*) and (*S*, *S*) ^{1}H-NMR ($CDCl_3$): δ 1.16 (d, 3H), 1.32 (t, 3H), 2.03 (m, 1H), 2.42 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.94 (m, 1H), 4.26 (m, 2H), 4.86 (m, 1H), 6.77 (s, 1H), 7.30 (s, 1H).

Preparations 19 and 20



[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-Carbamoyl-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-cyano-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (2.22gm, 7.32mmol, 1 eq) was dissolved in concentrated sulfuric acid (12mL) and water (0.66mL, 36.6mmol, 5 eq). After 12 hr at ambient temperature the reaction was quenched into solid sodium bicarbonate, dissolved in water and extracted 3 times with ethyl acetate. Organic layers were collected, dried over anhydrous sodium sulfate, filtered, and concentrated to provide the title compounds (2.25gm, 6.98mmol, 95% yield).

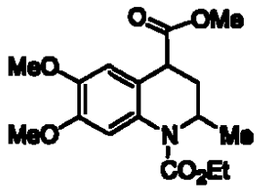
LCMS (ESI+): 323 (MH+).

[(*R*, *S*), (*S*, *R*)]: ^{1}H-NMR ($CDCl_3$): δ 1.20 (d, 3H), 1.30 (t, 3H), 1.89 (m, 1H), 2.41 (m, 1H), 3.37 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.22 (m, 2H), 4.55 (m, 1H), 5.70 (s, 1H), 5.80 (s, 1H), 6.70 (s, 1H), 7.21 (s, 1H).

LCMS (ESI+): 323 (MH+).

[(*R*, *R*), (*S*, *S*)]: ^{1}H-NMR ($CDCl_3$): δ 1.17 (d, 3H), 1.30 (t, 3H), 1.74 (m, 1H), 2.67 (m, 1H), 3.55 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.21 (m, 2H), 4.58 (m, 1H), 5.38 (s, 1H), 5.49 (s, 1H), 6.65 (s, 1H), 7.15 (s, 1H).

Preparations 21 and 22



[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-6,7-Dimethoxy-2-methyl-3, 4-dihydro-2H-quinoline-1,4-dicarboxylic acid-1-ethyl ester–4-methyl ester

[(*R*, *S*), ((*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-Carbamoyl-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (2.24gm, 6.95mmol, 1 eq) was placed in a 100mL round bottomed flask equipped with a stir bar and was dissolved in methylene chloride (56.5mL). Trimethyloxonium tetrafluoroborate (1.29gm, 8.76mmol, 1.26 eq) was added to the solution followed by 12.2mL more of methylene

chloride. After 12 hr at ambient temperature the reaction mixture was concentrated to dryness and used without further purification. The product (2.84gm, 6.95mmol, 1 eq) was dissolved in water (20mL) and stirred for several hours at room temperature. The mixture was saturated with sodium chloride solution, extracted 3 times with ethyl acetate, dried over sodium sulfate, filtered and concentrated to dryness. Flash chromatography eluting with 80/20 hexanes/ethyl acetate provided the title compounds (1.65gm, 4.88mmol, 70% yield).

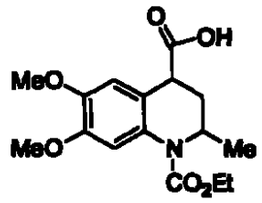
LCMS (ESI+): 338 (MH+).

[(*R*, *S*) (*S*, *R*)] ^{1}H-NMR ($CDCl_3$): δ 1.17 (d, 3H), 1.29 (t, 3H), 1.81 (m, 1H), 2.46 (m, 1H), 3.56 (m, 1H), 3 .81 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.21 (m, 2H), 4.55 (m, 1H), 6.60 (s, 1H), 7.11 (s, 1H).

LCMS (ESI+): 338 (MH+).

[(*R*, *R*) (*S*, *S*)]: ^{1}H-NMR ($CDCl_3$): δ 1.13 (d, 3H), 1.29 (t, 3H), 1.78 (m, 1H), 2.54 (m, 1H), 3.67 (s, 3H), 3.71 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.21 (m, 2H), 4.74 (m, 1H), 6.66 (s, 1H), 7.13 (s, 1H).

Preparations 23 and 24



[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-6,7-Dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester

[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-6,7-Dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1,4-carboxylic acid ethyl ester-4-methyl ester (0.62gm, 1.73mmol, 1 eq) was dissolved in dioxane (12mL) and water (12mL) in round bottomed flask with a magnetic stir bar. Sodium hydroxide (0.13gm, 3.48mmol, 2 eq) was added and stirred at room temperature. After 12 hr, the reaction mixture was concentrated and partitioned between 1.0 N aqueous sodium hydroxide and diethyl ether. The aqueous layer was collected, acidified with concentrated hydrochloric acid, and extracted with ether. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated to provide the title compounds (0.538gm, 1.65mmol, 90% yield) as a mixture of diastereoisomers.

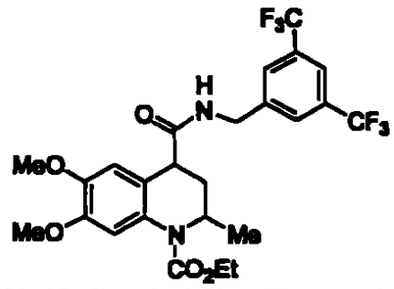
LCMS (ESI+): 324 (MH+).

[(*R*, *S*), (*S*, *R*)]: ^{1}H-NMR ($CDCl_3$): δ 1.18 (d, 3H), 1.30 (t, 3H), 1.89 (m, 1H), 2.48 (m, 1H), 3.61 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.21 (m, 2H), 4.60 (m, 1H), 6.75 (s, 1H), 7.15 (s, 1H).

LCMS (ESI+): 324 (MH+).

[(*R*, *R*), (*S*, *S*)]: ^{1}H-NMR ($CDCl_3$): δ 1.14 (d, 3H), 1.29 (t, 3H), 1.83 (m, 1H), 2.56 (m, 1H), 3.74 (m, 1H), 3.85 (s, 6H), 4.21 (m, 2H), 4.76 (m, 1H), 6.70 (s, 1H), 7.14 (s, 1H).

Examples 11 and 12



[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-6,7-Dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester (0.229gm, 0.710mmol) was placed in a 25mL round bottomed flask equipped with a stir bar. Methylene chloride (7.0mL) was added followed by the addition of 3,5-bis(trifluoromethyl)benzylamine (0.519gm, 2.14mmol, 3.0 eq). To this reaction, 1-hydroxybenzotriazole hydrate (0.022gm, 0.146mmol, 0.2 eq) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.232gm, 1.21mmol, 1.7 eq) were added. The reaction mixture was stirred at room temperature. After 12 hr, the reaction was quenched with water and extracted 3 times with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered, concentrated to provide the title compounds (0.1225gm, 0.223mmol, 58% yield) as a mixture of diastereoisomers.

LCMS (ESI+): 549 (MH+).

^{1}H NMR [(*R*, *R*), (*S*, *S*) and (*R*, *S*) (*S*, *R*)] ($CDCl_3$): δ 1.16 (d, 3H), 1.24 (t, 3H), 1.80 (m, 1H), 2.66 (m, 1H), 3.64 (m, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 4.11 (m, 2H), 4.29 (m, 1H), 4.56 (m, 2H), 4.70 (m, 2H), 6.05 (m, 1H), 6.40 (m, 1H), 6.65 (s, 1H), 6.60 (s, 1H), 7.13 (s, 1H), 7.66 (s, 2H), 7.75 (s, 1H), 7.80 (s, 1H). LCMS (ESI+): 549 (MH+).

Preparations 25 and 26

[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-6,7-Dimethoxy-4-(methoxymethyl-carbamoyl)-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-6,7-Dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester (0.536gm, 1.55mmol) was placed in a 25mL round bottomed flask equipped with a stir bar and dissolved in methylene chloride (10mL). The reaction mixture was cooled to 0 °C, and di-*iso*-propylethylamine (0.18gm, 2.0mmol, 1.3 eq) was added followed by addition of N,O-di-methylhydroxylamine hydrochloride (1.1 eq), 4-dimethylaminopyridine (0.1 eq), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.2 eq). The reaction mixture was stirred at room temperature. After 12 hr, the reaction mixture was quenched with water and extracted 3 times with ethyl acetate. The organic layers were collected, dried, filtered, and concentrated to provide the title compounds (0.56gm, 1.52mmol, 98% yield) that were used without further purification.

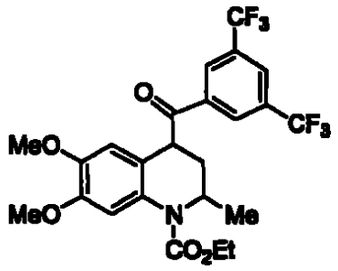
LCMS (ESI+): 367 (MH+).

[(*R*, *R*), (*S*, *S*)] ^{1}H-NMR ($CDCl_3$): δ 1.10 (d, 3H), 1.28 (t, 3H), 1.83 (m, 1H), 2.41 (m, 1H), 3.16 (s, 3H), 3.38 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.06 (m, 1H), 4.21 (m, 2H), 4.84 (m 1H), 6.55 (s, 1H), 7.16 (s, 1H).

LCMS (ESI+): 367 (MH+).

[(*R*, *S*), (*S*, *R*)] ^{1}H-NMR ($CDCl_3$): δ 1.32 (d, 3H), 1.65 (t, 3H), 1.75 (m, 1H), 2.39 (m, 1H), 3.16 (s, 3H), 3.35 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.06 (m, 1H), 4.21 (m, 2H), 4.84 (m 1H), 6.45 (s, 1H), 7.05 (s, 1H).

Examples 13 and 14



[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-6,7-Dimethoxy-4-(methoxy-methyl-carbamoyl)-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.56gm, 1.45mmol, 1 eq) was dissolved in tetrahydrofuran (12mL) in a round bottomed flask

equipped with a magnetic stir bar. The reaction was cooled to 0 °C. 3,5-Bis(trifluoromethyl)phenyl magnesium bromide (13.6mL of 0.5 M solution) was added drop wise, and the reaction mixture was stirred at room temperature. After 12 hr, the reaction mixture was quenched with aqueous ammonium chloride, further saturated with NaCl and extracted 3 times with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered and concentrated to dryness. Flash chromatography eluting with 90/10 hexanes/ethyl acetate provided the title compounds (0.556gm, 1.07mmol, 73% yield).

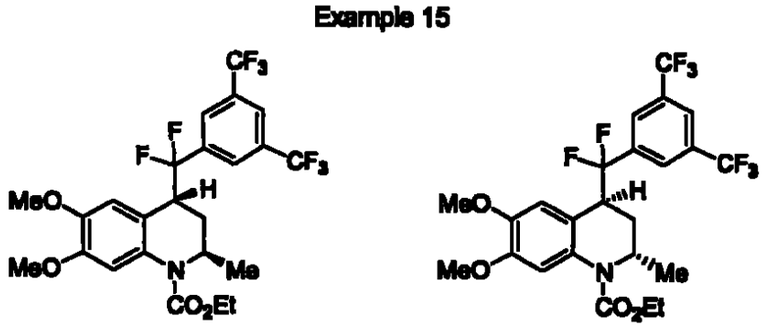
LCMS (ESI+): 520 (MH+).

[(*R*, *S*), (*S*, *R*)]: ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H), 1.35 (t, 3H), 1.81 (m, 1H), 2.52 (m, 1H), 3.63 (s, 3H), 3.88 (s, 3H), 4.29 (m, 2H), 4.42 (m, 1H), 4.57 (m, 1H), 6.21 (s, 1H), 7.15 (s, 1H), 8.13 (s, 1H), 8.45 (s, 2H).

LCMS (ESI+): 520 (MH+).

[(*R*, *R*), (*S*, *S*)] ^{1}H NMR ($CDCl_3$): δ 1.16 (d, 3H), 1.28 (t, 3H), 1.88 (m, 1H), 2.67 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.21 (m, 2H), 4.45 (t, 1H), 4.88 (m, 1H), 6.59 (s, 1H), 7.07 (s, 1H), 7.97 (s, 1H), 8.25 (s, 2H).

Example 15



[(*R*, *R*), (*S*, *S*)]- 4-(3,5-Bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-methyl-5,6-dimethoxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

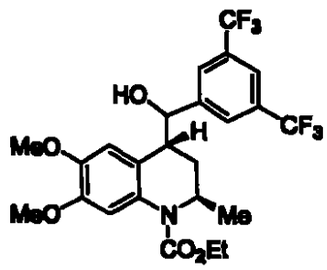
[(*R*, *R*), (*S*, *S*)]-4-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-6,7-dimethoxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.062gm, 0.120mmol) was dissolved in methylene chloride (0.25mL) in a vial equipped with a magnetic stir bar. [Bis(2-methoxyethyl)amino]sulfur trifluoride (0.22mL, 1.20mmol, 10 eq) was added to this solution and the reaction mixture was stirred at room temperature. After 12 hr, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted 3 times with ethyl acetate. The organic layers were collected, dried over magnesium sulfate, filtered, concentrated and purified by chromatography

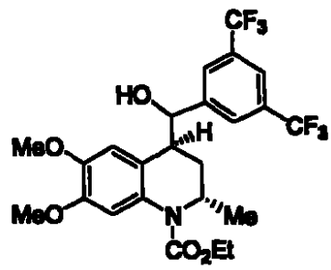
on silica eluting with 90/10 hexanes/ethyl acetate to provide the title compound (0.045gm, 0.08mmol, 66% yield).

LCMS (ESI+): 542 (MH+).

[(*R*, *R*), (*S*, *S*)]: ^{1}H NMR ($CDCl_3$): δ 1.10 (d, 3H), 1.22 (t, 3H), 1.95 (m, 1H), 2.45 (m, 1H), 3.55 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 4.00 (m, 1H), 4.19 (m, 1H), 4.60 (m, 1H), 6.45 (s, 1H), 6.99 (s, 1H), 7.8 (s, 2H), 7.90 (s, 1H).

Examples 16 and 17





[(*R*, *R*, *R*), (*S*, *S*, *S*)] and [(*R*, *R*, *S*), (*S*, *S*, *R*)]-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *R*), (*S*, *S*)]-4-(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.302gm, 0.58mmol, 1 eq) was placed in a round bottomed flask equipped with a magnetic stir bar. Methanol (12mL) was added followed by the addition of sodium borohydride (0.131gm, 3.48mmol, 6 eq) at room temperature. After 1 hour, the reaction mixture was quenched with a brine solution, extracted 3 times with ethyl acetate and dried over sodium sulfate. The material was purified by flash chromatography eluting with 75/25 hexanes/ethyl acetate to provide the title compounds (0.271gm, 0.52mmol, 89% yield).

Diastereoisomer 1 (29% yield)

LCMS (ESI+): 522 (MH+).

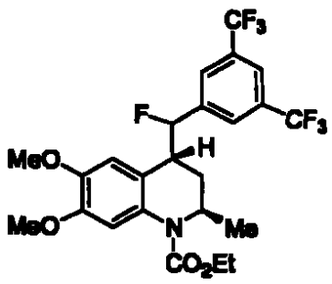
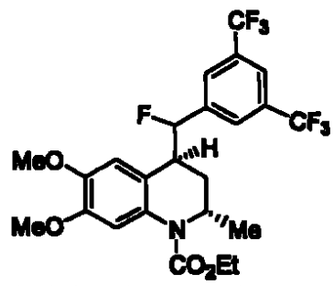
^{1}H NMR ($CDCl_3$): δ 1.12 (d, 3H), 1.29 (t, 3H), 1.39 (m, 1H), 2.52 (m, 1H), 2.81 (br s, 1H), 2.94 (m, 1H), 3.65 (s, 3H), 3.83 (s, 3H), 4.21 (m, 2H), 4.67 (m, 1H), 5.04 (d, 1H), 6.18 (s, 1H), 7.02 (s, 1H), 7.64 (s, 2H), 7.72 (s, 1H).

Diastereoisomer 2 (60% yield)

LCMS (ESI+): 522 (MH+).

^{1}H NMR ($CDCl_3$): δ 1.14 (d, 3H), 1.34 (t, 3H), 1.56 (m, 1H), 1.86 (m, 1H), 2.97 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.26 (m, 2H), 4.49 (m, 1H), 4.77 (d, 1H), 6.70 (s, 1H), 7.09 (s, 1H), 7.84 (s, 3H).

Examples 18 and 19

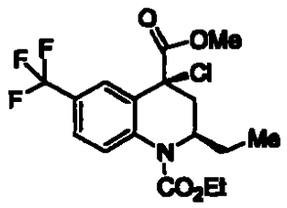
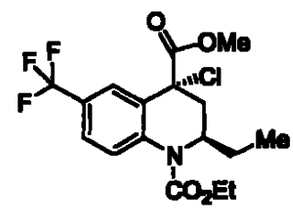
[(*R*, *R*, *R*), (*S*, *S*, *S*) and (*R*, *R*, *S*), (*S*, *S*, *R*)]-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *R*, *R*), (*S*, *S*, *S*) and (*R*, *R*, *S*), (*S*, *S*, *R*)]-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.06gm, 0.115mmol) was placed in a small round bottomed flask containing a magnetic stir bar and dissolved in dichloromethane (0.25mL). To this reaction, (diethylamino)sulfur trifluoride (0.152mL) was added dropwise at room temperature. After 2 hr, the reaction was quenched with the addition of aqueous ammonium chloride solution and extracted 3 times with EtOAc. Organics were collected, dried over Na_2SO_4, filtered and concentrated to afford the title compounds in 40% isolated yield (0.024gm, 0.046mmol).

LCMS (ESI+): 524 (MH+).

^{1}H NMR ($CDCl_3$): δ 1.19 (d, 3H), 1.30 (t, 3H), 2.02 (m, 1H), 2.95 (m, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.26 (m, 2H), 4.49 (m, 1H), 6.40 (s, 1H), 6.9 (s, 1H), 7.1 (s, 1H), 7.8 (s, 3H), 7.95 (s, 1H).

Preparation 27

[(*R*, *S*) and (*R*, *R*)]-4-Chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4-methyl ester

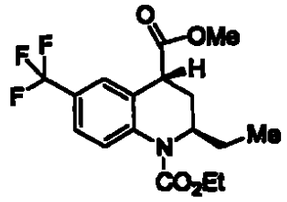
(*R*)-2-Ethyl-4-hydrazono-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (Preparation 6, 1.22gm, 3.70mmol) was placed in a 250mL round bottomed flask equipped with a stir bar. Diethyl ether (100mL) was added followed by the addition of MnO_2 (22.2mmol, 6 eq). The reaction was

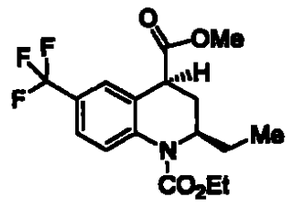
protected from light and stirred at room temperature for 90 min. The solution was filtered through Celite® and concentrated to a final volume of 30mL. Additional toluene (100mL) was added and concentrated to 40mL. To this solution was added of di-iso-propylethylamine (3.25mL, 18.5mmol), followed by the addition of 20% phosgene solution in toluene (7.5mL). The reaction mixture was stirred for 45 min before anhydrous methanol (10mL) was added. After 2 hr, the reaction was concentrated down to 20mL, extracted into methylene chloride and washed with 0.1 N HCl. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated to dryness to obtain the title compound (1.43gm, 3.66mmol, 98% yield).

LCMS (ESI+): 394 (MH+).

(*R*, *S*), (*R*, *R*): ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H), 1.25 (m, 2H), 1.30 (t, 3H), 2.60 (dd, 1H), 2.79 (dd, 1H), 3.99 (s, 3H), 4.23 (m, 2H), 4.62 (m, H), 7.61 (d, 1H), 7.70 (d, 1H).

Preparation 28 and 29





Preparation of [(*R*, *S*) and (*R*, *R*)]-2-Ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4-methyl ester [(R, S) and (*R*, *R*)]-4-Chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4 methyl ester (1.40 grams, 3.56 mmol) was dissolved in 30 mL of methanol before 0.15 grams of 10% Pd/C was added and the mixture was hydrogenated at 45 psi on the par shaker for 2 hours. The reaction mixture was filtered through Celite and concentrated. The crude mixture was then dissolved in dichloromethane and the organics were collected, dried over magnesium sulfate and concentrated. The product was isolated after purification by column chromatography eluting with a solution of 90:10 hexane-acetone to yield 83% (2.98 mmol) of the title compound.

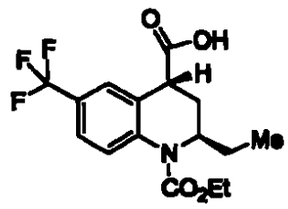
(*R*, *S*): ^{1}H NMR ($CDCl_3$): δ? 0.84 (t, 3H), 1.30 (t, 3H), 1.40 (m, 2H), 1.95 (m, 1H), 2.47 (m, 1H), 3.61 (m, 1H), 3.80 (s, 3 H), 4.3 (m, 2H), 4.42 (m, 1H), 7.40 (s, 1H), 7.60 (d, 1H), 7.70 (d, 1H).

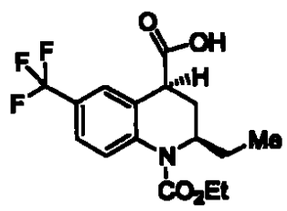
LCMS (ESI+): 360 (MH+)

(*R*, *R*): ^{1}H NMR ($CDCl_3$): δ? 0.86 (t, 3H), 1.28 (t, 3H), 1.38 (m, 2H), 2.1 (m, 1H), 2.56 (m, 1H), 3.69 (s, 3H), 3.90 (t, 1H), 4.30 (m, 2H), 4.58 (m, 1H). 7.46 (s, 1H), 7.50 (d, 1H), 7.70 (d, 1H)

LCMS (ESI+): 360 (MH+)

Preparation 30





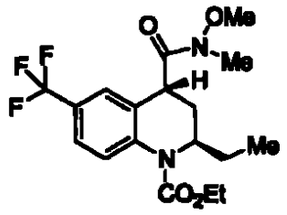
[(*R*, *S*) and (*R*, *R*)]-2-Ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester

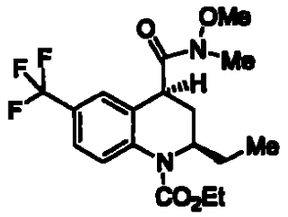
[(*R*, *S*) and (*R*, *R*)]-2-Ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester-4-methyl ester (Preparation 28 and 29, 0.070gm, 0.195mmol, 1 eq) was dissolved in a round bottomed flask with magnetic stir bar containing dioxane (1.5mL) and water (1.5mL). Sodium hydroxide (0.016gm, 0.409mmol, 2.1 eq) was added and stirred at room temperature. After 12 hr, the reaction mixture was concentrated to a minimum volume and partitioned between 1.0 N aqueous sodium hydroxide and diethyl ether. The aqueous layer was collected, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic layer was collected, dried over magnesium sulfate, filtered and concentrated to provide the title compounds (0.067gm, 0.194mmol, 99% yield).

LCMS (ESI+): 346 (MH+).

[(*R*, *S*), (*R*, *R*)]: ^{1}H-NMR ($CDCl_3$): δ 0.84 (t, 3H), 1.23 (t, 3H), 1.39 (m, 2H), 1.94 (m, 1H), 2.59 (m, 1H), 3.84 (t, 1H), 4.19 (m, 2H), 4.62 (m, H), 7.49 (m, 2H), 7.63 (d, 1H).

Preparation 31





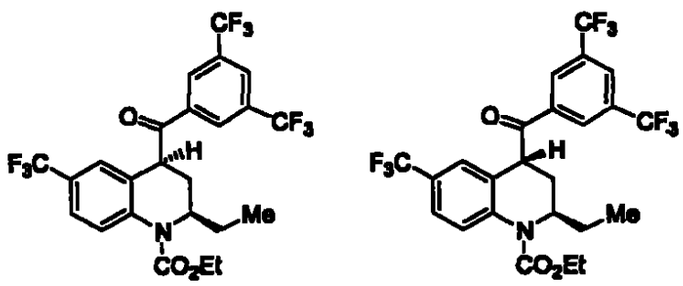
[(*R*, *S*) and (*R*, *R*)]-2-Ethyl-4-(methoxy-methyl-carbamoyl)-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*) and (*R*, *R*)]-2-Ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1,4-dicarboxylic acid-1-ethyl ester (0.088gm, 0.239mmol) was placed in a 5mL round bottomed flask equipped with stir bar. Methylene chloride (3mL) was added. The reaction mixture was cooled to 0 °C. Di-iso-propylethylamine (0.032gm, 0.248mmol, 1.3 eq) was added followed by addition of *N*,*O*-dimethylhydroxylamine HCl salt (0.239mmol), 4-dimethylaminopyridine (0.019mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.210mmol). The reaction was stirred at room temperature. After 12 hr, the reaction was quenched with water and extracted 3 times with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered, concentrated to provide the title compounds (0.065gm, 0.167mmol, 88% yield).

LCMS (ESI+): 389 (MH+).

[(*R*, *S*), (*R*, *R*)]: ^{1}H-NMR ($CDCl_3$): δ 0.90 (t, 3H), 1.33 (t, 3H), 1.39 (m, 2H), 2.0 (m, 1H), 2.55 (m, 1H), 3.20 (s, 3H), 3.40 (s, 3H), 4.19 (m, 2H), 4.62 (m, 1H), 7.21 (s, 1H), 7.40 (s, 2H), 7.62 (d, 2H).

Examples 20 and 21



[(*R*, *S*)] and [(*R*, *R*)]-4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*), (*R*, *R*)]-2-Ethyl-4-(methoxy-methyl-carbamoyl)-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.564gm 1.45mmol, 1 eq) was dissolved in tetrahydrofuran (12mL) in a round bottomed flask equipped with a stir bar. The reaction was cooled to 0 °C. 3,5-Bis(trifluoromethyl)phenyl magnesium bromide (13.6mL of 0.5M solution) was added dropwise, and the reaction mixture was stirred at room temperature. After 12 hr, the reaction mixture was quenched with aqueous ammonium chloride solution, further saturated with NaCl and extracted 3 times with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered and concentrated to dryness. Flash chromatography eluting with

90/10 hexanes/ethyl acetate provided the title compounds (0.556gm, 1.02mmol, 70% yield).

trans isomer:

LCMS (ESI+): 542 (MH+).

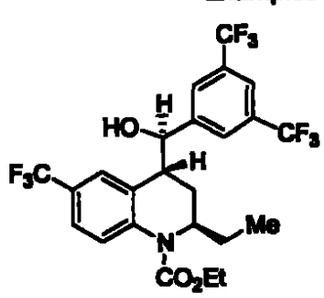
(*R*, *R*): ^{1}H-NMR ($CDCl_3$): δ 0.98 (t, 3H), 1.29 (t, 3H), 1.52 (m, 2H), 2.05 (m, 1H), 2.64 (m, 1H), 4.24 (m, 2H), 4.66 (m, 2H), 7.40 (s, 1H), 7.55 (d, 1H), 7.60 (d, 1H), 8.05 (s, 2H), 8.24 (s, 1H).

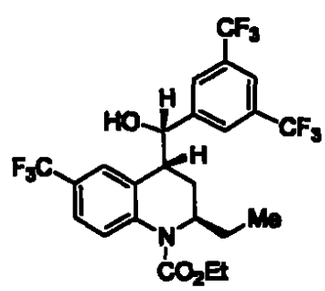
cis isomer:

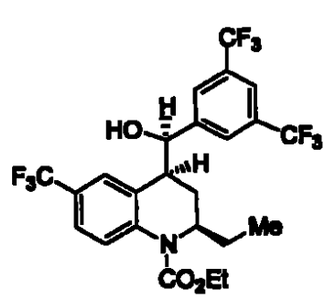
LCMS (ESI+): 542 (MH+).

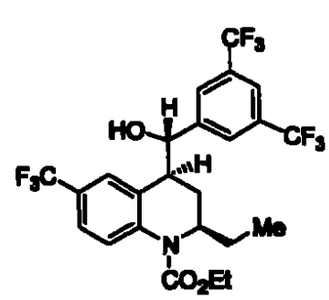
(*R*, *S*): ^{1}H-NMR ($CDCl_3$): δ 0.91 (t, 3H), 1.39 (t, 3H), 1.43 (m, 2H), 1.78 (m, 1H), 1.99 (m, 1H), 2.60 (m, 1H), 4.34 (m, 2H), 4.58 (m, 2H), 7.05 (s, 1H), 7.55 (d, 1H), 7.65 (d, 1H), 8.20 (s, 1H), 8.44 (s, 2H).

Examples 22, 23, 24 and 25









[(*R*, *R*, *R*)], [(*R*, *R*, *S*)], [(*R*, *S*, *S*)], and [(*R*, *S*, *R*)]-4-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid *ethyl ester*

[(*R*, *S*)] and [(*R*, *R*)]-4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.182gm, 0.34mmol, 1 eq) was placed in a round bottomed flask equipped with a magnetic stir bar. Methanol (6.8mL) was added followed by the addition of (0.077gm, 2.05mmol, 6

eq) sodium borohydride at room temperature. After 1 hour, the reaction mixture was quenched with brine solution, extracted 3 times with ethyl acetate and dried over sodium sulfate. The material was purified by flash chromatography eluting with 90/10 hexanes/ethyl acetate to provide the title compounds in three fractions.

(R,S,R):

LCMS (ESI+): 544 (MH+).

^{1}H-NMR ($CDCl_3$): δ 0.81 (t, 3H), 1.27 (t, 3H), 2.04 (m, 1H), 4.22 (m, 3H), 7.86 (s, 1H), 7.90 (s, 1H).

(R,S,S):

LCMS (ESI+): 544 (MH+).

^{1}H-NMR ($CDCl_3$): δ 0.73 (t, 3H), 1.09 (m, 1H), 1.27 (t, 3H), 1.43 (m, 2H), 1.67 (m, 1H), 2.44 (d, 1H), 2.87 (m, 1H), 4.24 (m, 3H), 5.17 (dd, 1H), 7.26 (s, 1H), 7.50 (m, 2H), 7.90 (s, 2H), 7.92 (s, 1H).

(R,R,R) and (R,R,S): This mixture was separated on a 10 cm by 50 cm, Chiralpak AD column eluting in heptane/IPA 98//2 at a flow rate of 275 mL/min.

(R,R,R): ^{1}H-NMR ($CDCl_3$): δ 0.77 (t, 3H), 1.31 (t, 3H), 1.41 (m, 2H), 2.21 (d, 1H), 3.19 (m, 1H), 4.23 (m, 2H), 4.37 (m, 1H), 4.83 (d, 1H), 7.65 (s, 2H), 7.79 (s, 1H).

LCMS (ESI+): 544 (MH+).

(R,R,S): ^{1}H-NMR ($CDCl_3$): δ 0.81 (t, 3H), 1.33 (t, 3H), 1.6 (m, 2H), 2.22 (d, 1H), 3.05 (m, 1H), 4.30 (m, 2H), 4.62 (m, 1H), 5.19 (d, 1H), 7.01 (s, 1H), 7.40 (s, 2H), 7.85 (s, 1H).

LCMS (ESI+): 544 (MH+).

Preparations 32 and 33

[(*R*, *R*), (*S*, *S*)] and [(*S*, *R*), (*R*, *S*)]-4-Aminomethyl-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

Sodium borohydride (0.828gm, 21.9mmol) was suspended in tetrahydrofuran (13.5mL) in a dry 50mL round-bottomed flask equipped with stir bar. In another flask trifluoroacetic acid (1.68mL, 21.8mmol) was dissolved in tetrahydrofuran (5mL). The 50mL reaction flask was cooled to 0°C and the trifluoroacetic acid solution was added slowly. The reaction was allowed to stir at room temperature. After 30 min, [(*R*, *R*), (*S*, *S*)] and [(*S*, *R*), (*R*, *S*)]-4-cyano-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (1.33gm, 4.37mmol) in tetrahydrofuran (5mL) was added drop wise to the reaction. After 12 hr, the reaction was cooled back to 0 °C and

carefully quenched with water. The aqueous layer was extracted 2 times with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 97/2/1 methylene chloride/methanol/triethylamine to afford the title compounds (0.982gm, 3.18mmol, 73% yield).

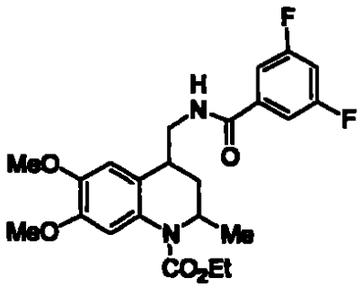
LCMS (ESI+): 309 (MH+).

[*(R, S), (S, R)*] ^{1}H-NMR ($CDCl_3$): δ 1.18 (d, 3H), 1.27 (t, 3H), 2.47 (m, 2H), 2.92 (m, 1H), 3.29 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.19 (m, 2H), 4.47 (m, 1H), 6.69 (s, 1H), 7.02 (s, 1H).

LCMS (ESI+): 309 (MH+).

[*(R, R), (S, S)*] ^{1}H-NMR ($CDCl_3$): δ1.15 (d, 3H), 1.31 (t, 3H), 1.76 (m, 1H), 2.18 (m, 1H), 2.94 (m, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.22 (m, 2H), 4.61 (m, 1H), 6.69 (s, 1H), 7.12 (s, 1H).

Example 26



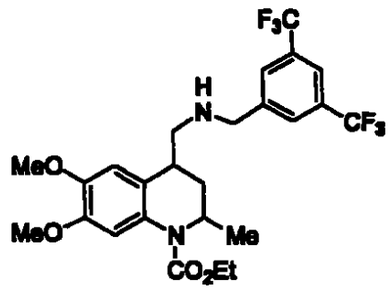
[(*R, S*), (*R, R*)] and [(*S, S*), (*S, R*)]-4-[(3,5-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

To a solution of [(*R, S*), (*R, R*)] and [(*S, S*), (*S, R*)]-4-aminomethyl-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.012gm, 0.039mmol) in methylene chloride (1.0mL) was added 3,5-difluorobenzoic acid (0.0065gm, 0.041mmol, 1.0 eq) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.012gm, 0.065mmol, 1.6 eq) and 1-hydroxybenzotriazole hydrate (0.005gm, 0.039mmol, 1 eq). The reaction was stirred at ambient temperature for 12 hr. The mixture was concentrated, dissolved in dimethylsulfoxide and purified by HPLC to provide the title compound (0.008gm, 0.019mmol).

LCMS (ESI+): 449 (MH+).

[(*R*, *S*), (*R*, *R*)] and [(*S*, *S*), (*S*, *R*)]: ^{1}H-NMR ($CDCl_3$): δ 1.15 (d, 3H), 1.30 (t, 3H), 1.79 (m, 1H), 2.16 (m, 1H), 3.16 (m, 1H), 3.63 (m, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 4.22 (m, 2H), 4.63 (m, 1H), 6.13 (m, 1H), 6.63 (s, 1H), 6.82 (m, 1H), 7.13 (s, 1H), 7.19 (m, 2H).

Examples 27 and 28



[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-[(3,5-Bis-trifluoromethyl-benzylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*), (*S*, *R*)] and [(*S*, *S*), (*R*, *R*)]-4-Aminomethyl-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.131gm, 0.428mmol) was dissolved in dichloroethane (2.0mL) in a 10mL round bottomed flask equipped with a stir bar. To this solution, 3,5-bis(trifluoromethyl)benzaldehyde (0.071mL, 0.431mmol) was added followed by sodium triacetoxyborohydride (0.272gm, 1.28mmol). After stirring at ambient temperature for 12 hr, the reaction mixture was quenched with a 1.0 N aqueous sodium hydroxide solution and extracted 3 times with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography eluting with 80/20 hexanes/ethyl acetate provided the title compounds (0.063gm, 0.12mmol, 28% yield).

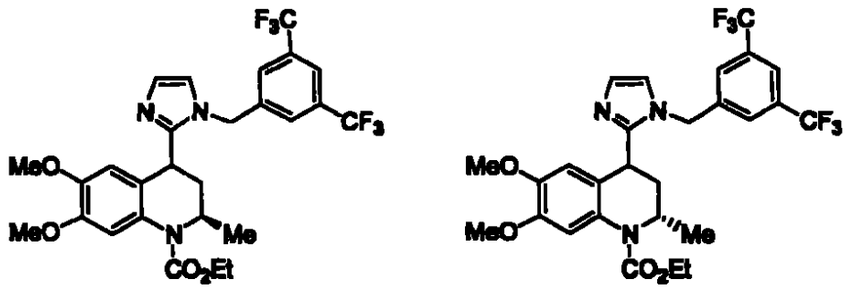
LCMS (ESI+): 535 (MH+).

[(*R*, *S*) (*S*, *R*)] ^{1}H-NMR ($CDCl_3$): δ 1.09 (m, 1H), 1.17 (d, 3H), 1.28 (t, 3H), 2.47 (m, 1H), 2.61 (m, 1H), 2.83 (m, 1H), 3.16 (m, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 4.02 (s, 2H), 4.20 (m, 2H), 4.47 (m, 1H), 6.81 (s, 1H), 7.01 (s, 1H), 7.82 (s, 1H), 7.87 (s, 2H).

LCMS (ESI+): 535 (MH+).

[(*R*, *R*) (*S*, *S*)] ^{1}H-NMR ($CDCl_3$): δ 1.14 (d, 3H), 1.28 (t, 3H), 1.74 (m, 1H), 2.21 (m, 1H), 2.79 (m, 2H), 2.93 (m, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 3.88 (s, 2H), 4.20 (m, 2H), 4.56 (s, 1H), 6.69 (s, 1H), 7.11 (s, 1H), 7.75 (s, 1H), 7.79 (s, 2H).

Examples 29 and 30



[(*R*, *S*), (*S*, *R*)] and [(*R*, *R*), (*S*, *S*)]-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

[(*R*, *S*), (*S*, *R*)] and [(*S*, *S*), (*R*, *R*)]-4-[(3,5-Bis-trifluoromethyl-benzylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.020gm, 0.037mmol) was dissolved in tetrahydrofuran (2.0mL) in a 10mL round bottomed flask equipped with a stir bar. To this solution, potassium carbonate (0.134gm, 0.972mmol) was added followed by the addition of methyl chloroformate (0.030mL, 0.388mmol). The reaction mixture was stirred at room temperature. After 12 hr, the reaction mixture was quenched with 1.0 N aqueous sodium hydroxide and extracted 3 times with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography eluting with 65/35 hexanes/ethyl acetate provided the title compounds (0.005gm, 0.008mmol, 30% yield).

LCMS (ESI+): 593 (MH+).

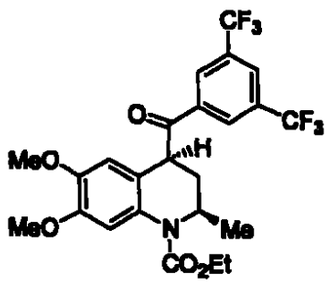
(*R*, *S*) (*S*, *R*)] ^{1}H-NMR ($CDCl_3$): δ 1.17 (d, 3H), 1.29 (t, 3H), 2.30 (m, 1H), 2.75 (m, 1H), 3.60 (m, 1H), 3.78 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.22 (m, 2H), 4.39 (m, 1H), 7.03 (s, 1H).

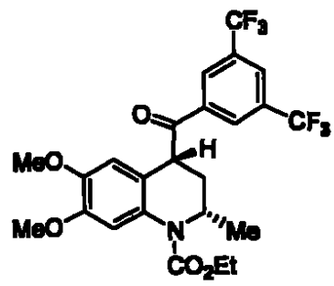
LCMS (ESI+): 593 (MH+).

[(*R*, *R*) (*S*, *S*)] ^{1}H-NMR ($CDCl_3$): δ 1.15 (d, 3H), 1.24 (m, 3H), 1.63 (m, 1H), 2.15 (m, 1H), 3.78 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.17 (m, 2H), 4.53 (m, 1H), 7.06 (s, 1H).

The following examples were prepared from analogous starting materials using methods analogous to those described in the examples above:

Example 31



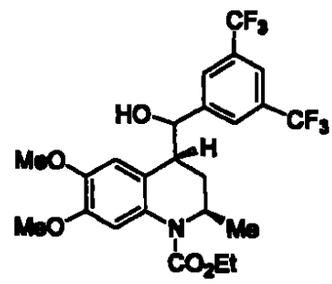


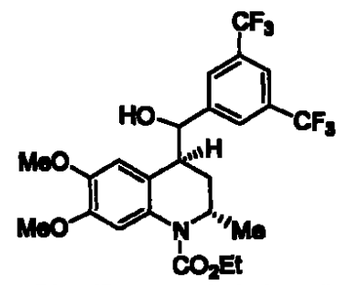
[(*R*, *S*), (*S*, *R*)]-4-[(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 1.2 (d, 3H), 1.35 (t, 3H), 1.95 (m, 1H), 2.55 (m, 1H), 3.80 (s, 3H), 3.97 (s, 3H), 4.20 (m, 1H), 4.22 (m, 1H), 4.40 (m, 1H), 4.62 (m, 1H), 6.2 (s, 1H), 7.1 (s, 1H) 8.19 (s, 1H), 8.45 (s, 2H).

LCMS (ESI+): 522 (MH+).

Example 32



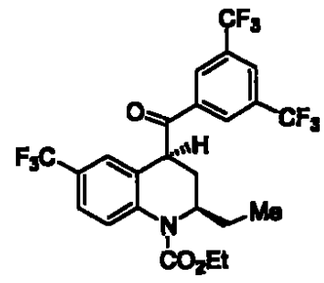


[(*R*, *S*, *S*), (*S*, *R*, *R*), (*R*, *S*, *R*), (*S*, *R*, *S*)]-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 1.13 (d, 3H), 1.34 (t, 3H), (m, 1H), 2.97 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.26 (m, 2H), 4.40 (m, 1H), 5.05 (d, 1H), 6.89 (s, 1H), 6.99 (s, 1H), 7.84 (s, 3H).

LCMS (ESI+): 522 (MH+).

Example 33

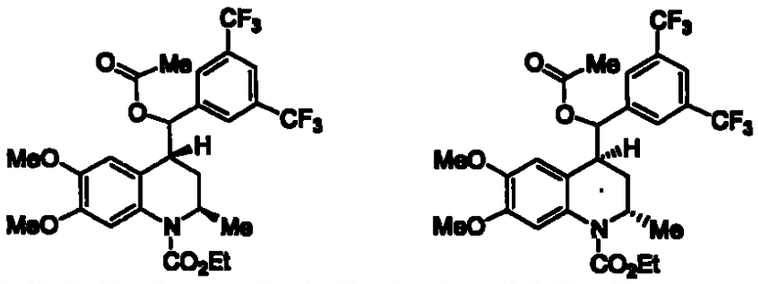


(*R, S*)-4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

(*R, S*)]- *cis*: ^{1}H-NMR ($CDCl_3$): δ 0.91 (t, 3H), 1.39 (t, 3H), 1.43 (m, 2H), 1.78 (m, 1H), 1.99 (m, 1H), 2.60 (m, 1H), 4.34 (m, 2H), 4.56 (m, 2H), 7.05 (s, 1H), 7.55 (d, 1H), 7.65 (d, 1H), 8.20 (s, 1H), 8.44 (s, 2H).

LCMS (ESI+): 542 (MH+).

Example 34

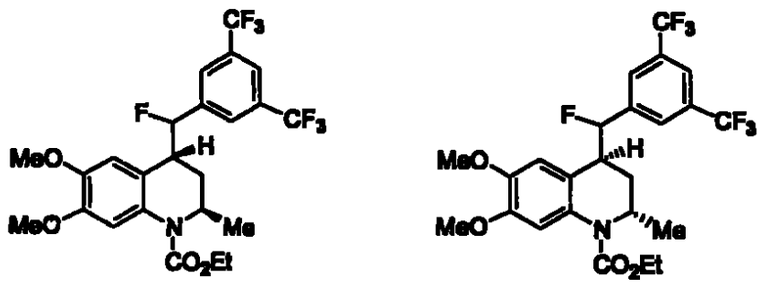


[(*R, R, S*), (*S, S, R*), (*R, R, R*), (*S, S, S*)]-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 1.10 (d, 3H), 1.29 (t, 3H), 1.62 (m, 1H), 1.87 (m, 1H), 2.00 (s, 3H), 3.22 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.21 (m, 2H), 4.47 (m, 1H), 5.89 (d, 1H), 6.62 (s, 1H), 7.03 (s, 1H), 7.66 (s, 2H), 7.80 (s, 1H).

LCMS (ESI+): 564 (MH+).

Example 35

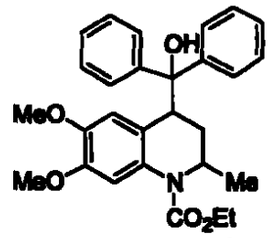


[(R,R,R) (S,S,S) and (R,R,S) and (S,S,R)]-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 1.19 (d, 3H), 1.30 (t, 3H), 2.02 (m, 1H), 2.95 (m, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.26 (m, 2H), 4.49 (m, 1H), 6.40 (s, 1H), 6.9 (s, 1H), 7.1 (s, 1H), 7.8 (s, 3H), 7.95 (s, 1H).

LCMS (ESI+): 524 (MH+).

Example 36

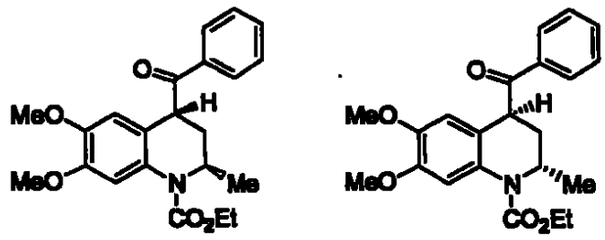


[(*R*, *R*), (*S*, *S*), (*R*, *S*), (*S*, *R*)]-4-(Hydroxy-diphenyl-methyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 1.0 (d, 3H), 1.32 (t, 3H), 2.2 (m, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.26 (m, 2H), 4.6 (m, 1H), 6.60 (s, 1H), 6.9 (s, 1H), 7.0 (s, 1H), 7.2-7.4 (m, 10H).

LCMS (ESI+): 444 (MH+) (minus 17 OH group).

Example 37

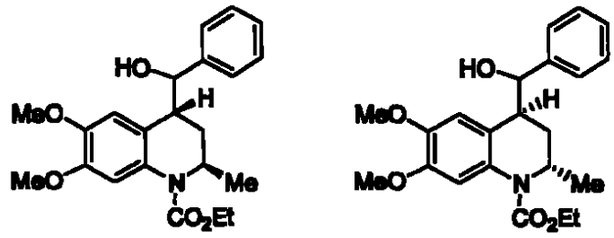


[(*R*, *R*), (*S*, *S*)-4-benzoyl-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 1.19 (d, 3H), 1.25 (t, 3H), 2.4 (m, 1H), 3.75 (s, 3H), 3.85 (s, 3H), 4.30 (m, 2H), 4.6 (m, 1H), 4.9 (m, 1H), 6.50 (s, 1H), 7.2 (s, 1H), 7.4 (m, 2H), 7.5 (t, 1H), 7.9 (d, 2H).

LCMS (ESI+): 384 (MH+).

Example 38



[(*R*, *S*, *S*), (*R*, *S*, *R*), (*S*, *R*, *R*), (*S*, *R*, *S*)] 4-(Hydroxy-phenyl-methyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

LCMS (ESI+): 386(MH+)

Examples 39-169 in Table A were prepared as racemic mixtures using analogous methods as described above from the appropriate starting materials and have the following structure:

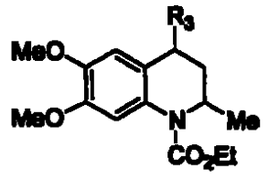
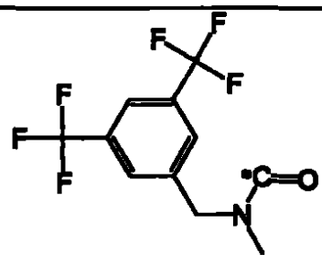
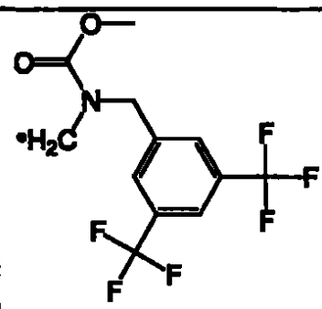
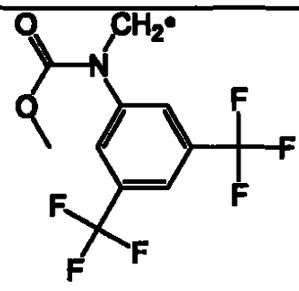
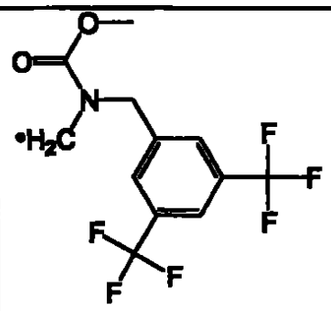
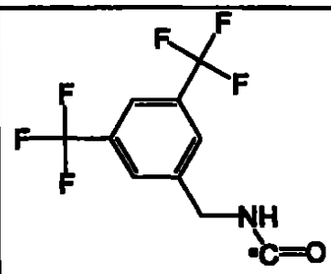
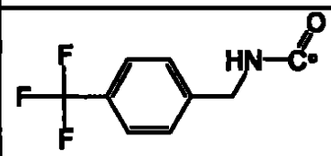
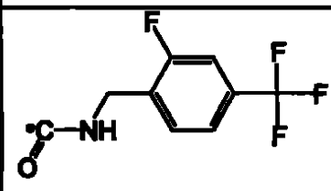
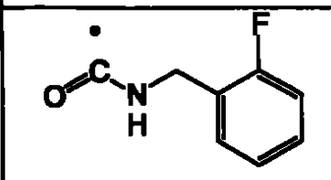
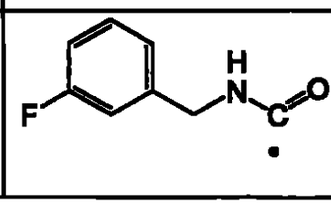
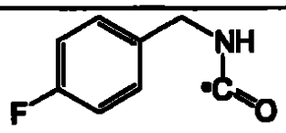
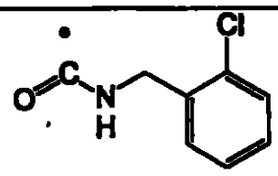
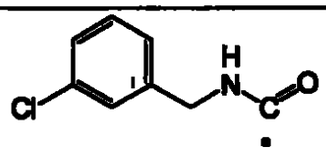
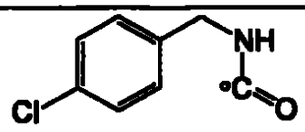
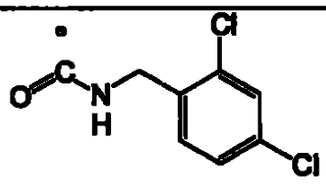
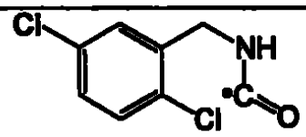
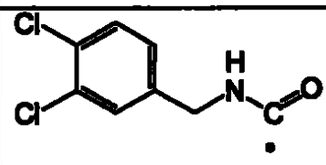
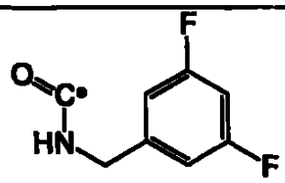
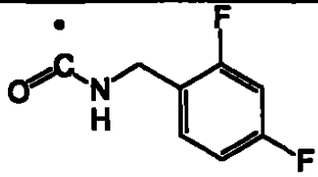
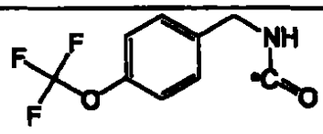
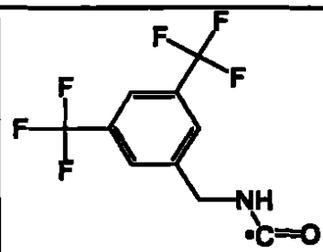
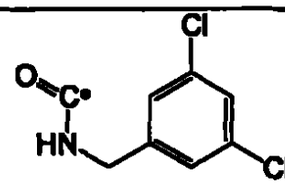
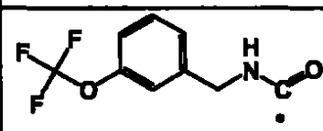


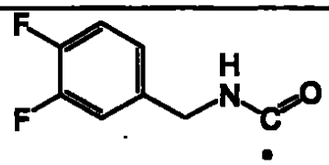
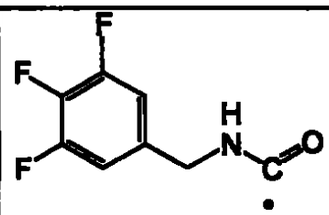
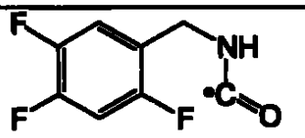
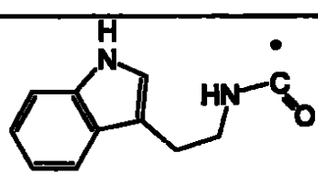
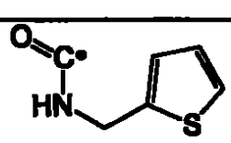
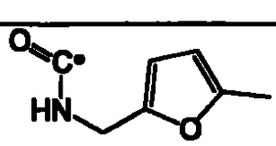
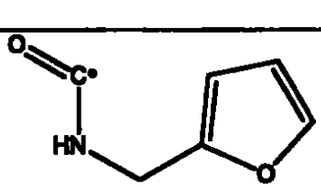
Table A

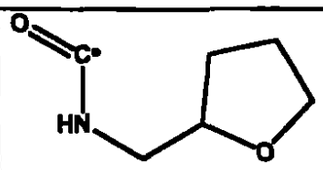
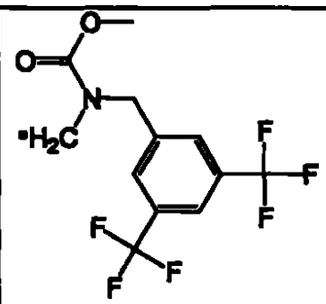
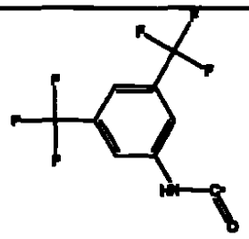
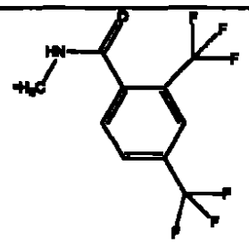
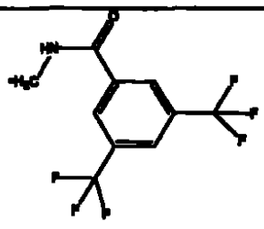
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
39		(4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester)	583
40		4-[[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	593
41		4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxy-carbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	579

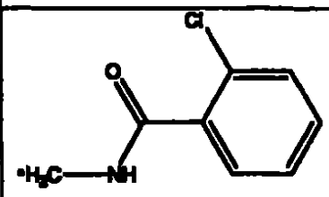
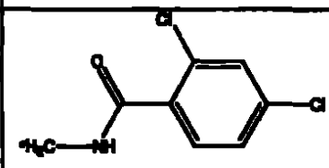
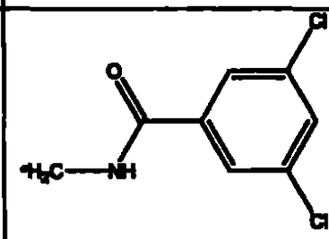
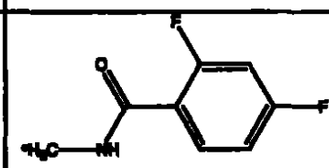
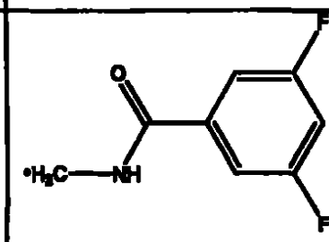
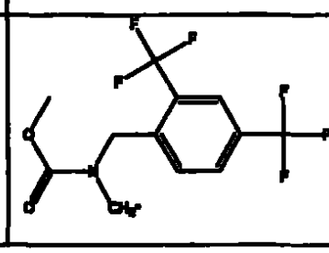
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
42		4-[[(3,5-Bis-trifluoromethyl-benzyl)-methoxy-carbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	593
43		4-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	549
44		6,7-Dimethoxy-2-methyl-4-(4-trifluoromethyl-benzylcarbamoyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
45		4-(2-Fluoro-4-trifluoromethyl-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499
46		4-(2-Fluoro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	431
47		4-(3-Fluoro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	431

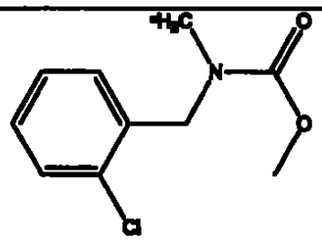
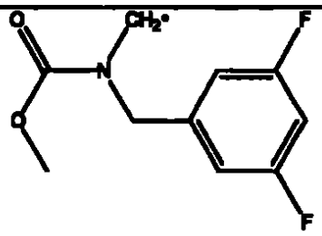
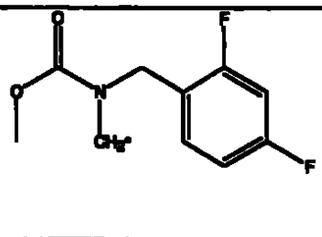
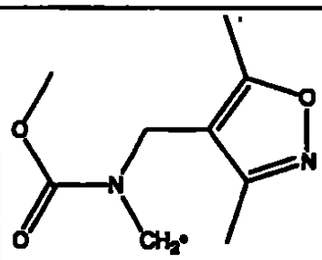
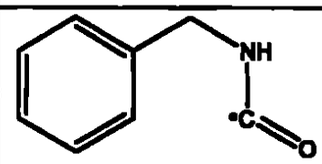
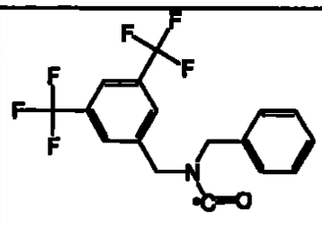
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
48		4-(4-Fluoro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	431
49		4-(2-Chloro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	447
50		4-(3-Chloro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	447
51		4-(4-Chloro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	447
52		4-(2,4-Dichloro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
53		4-(2,5-Dichloro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
54		4-(3,4-Dichloro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481

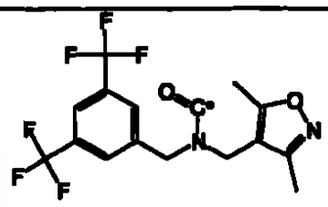
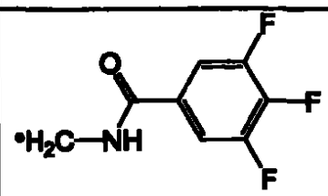
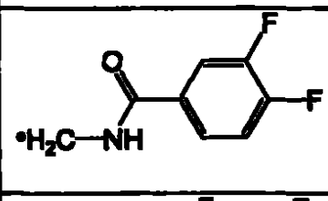
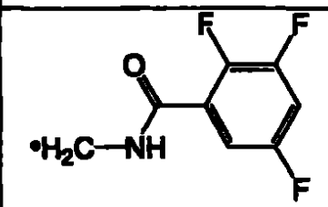
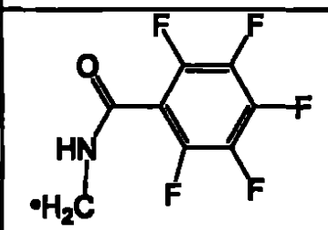
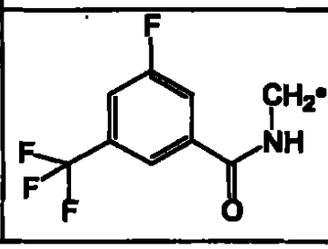
Ex.	R³ (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
55		4-(3,5-Difluoro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	449
56		4-(2,4-Difluoro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	449
57		6,7-Dimethoxy-2-methyl-4-(4-trifluoromethoxy-benzylcarbamoyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	497
58		4-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	549
59		4-(3,5-Dichloro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
60		6,7-Dimethoxy-2-methyl-4-(3-trifluoromethoxy-benzylcarbamoyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	497

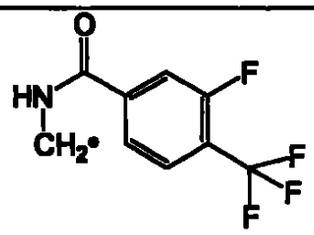
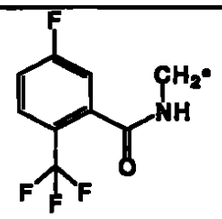
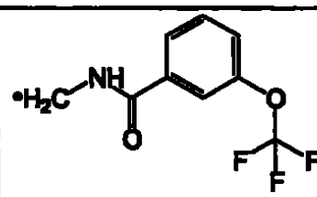
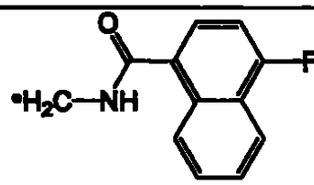
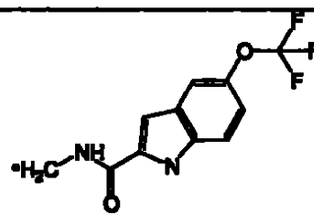
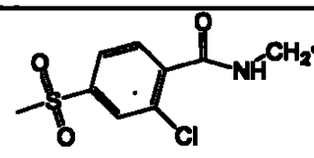
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
61		4-(3,4-Difluoro-benzylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	449
62		6,7-Dimethoxy-2-methyl-4-(3,4,5-trifluoro-benzylcarbamoyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	467
63		6,7-Dimethoxy-2-methyl-4-(2,4,5-trifluoro-benzylcarbamoyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	467
64		4-[2-(1H-Indol-3-yl)-ethylcarbamoyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	466
65		6,7-Dimethoxy-2-methyl-4-[(thiophen-2-ylmethyl)-carbamoyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	419
66		6,7-Dimethoxy-2-methyl-4-[(5-methyl-furan-2-ylmethyl)-carbamoyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	417
67		4-[(Furan-2-ylmethyl)-carbamoyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	403

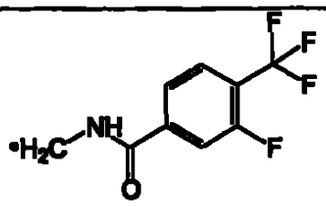
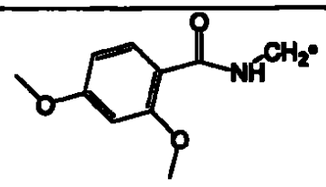
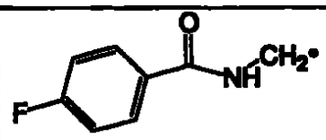
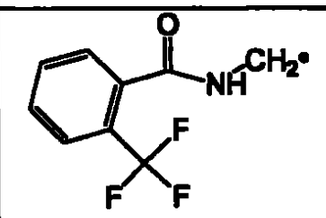
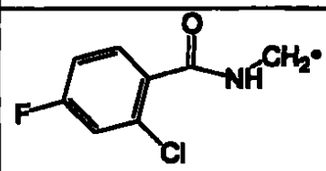
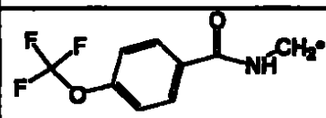
Ex.	R^3 (* denotes link to structure)	Compound	LCMS ESI+ (MH+)
68		6,7-Dimethoxy-2-methyl-4-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	407
69		4-[[(3,5-Bis-trifluoromethyl-benzyl)-methoxy-carbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-*2H*-quinoline-1-carboxylic acid ethyl ester	593
70		4-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	535
71		4-[(2,4-Bis-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	549
72		4-[(3,5-Bis-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	549

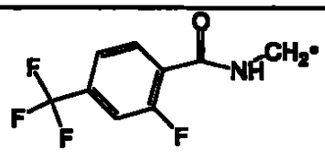
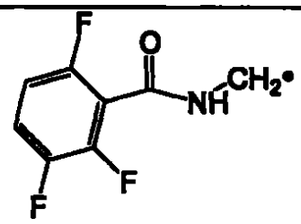
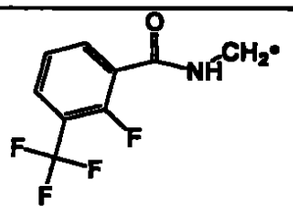
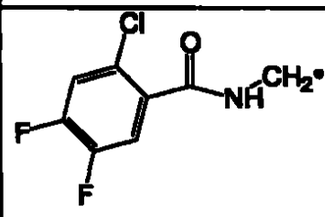
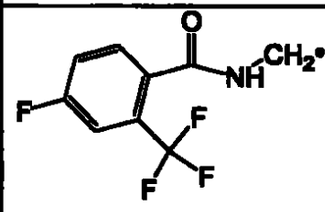
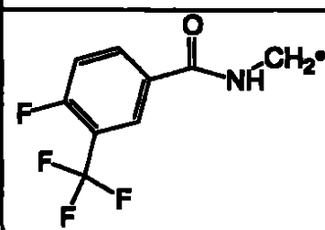
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
73		4-[(2-Chloro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	447
74		4-[(2,4-Dichloro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
75		4-[(3,5-Dichloro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
76		4-[(2,4-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	449
77		4-[(3,5-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	449
78		4-[[(2,4-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	593

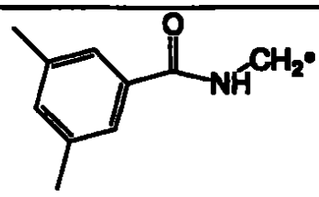
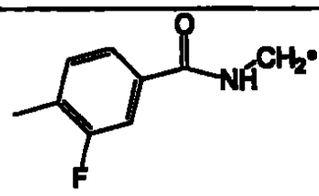
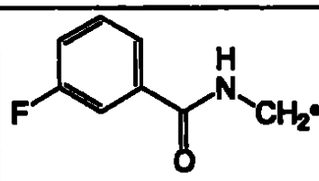
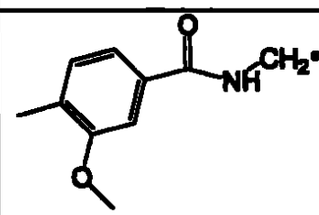
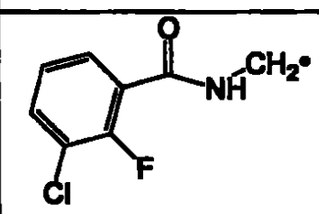
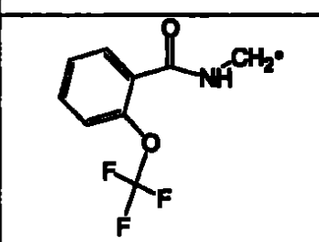
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
79		4-[[(2-Chloro-benzyl)-methoxycarbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	491
80		4-[[(3,5-Difluoro-benzyl)-methoxycarbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	493
81		4-[[(2,4-Difluoro-benzyl)-methoxycarbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	493
82		4-[[(3,5-Dimethyl-isoxazol-4-ylmethyl)-methoxycarbonyl-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	478
83		4-Benzylcarbamoyl-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	413
84		4-[Benzyl-(3,5-bis-trifluoromethyl-benzyl)-carbamoyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	639

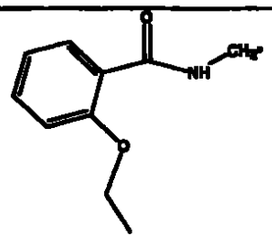
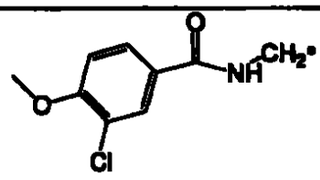
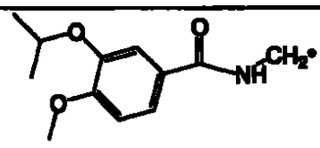
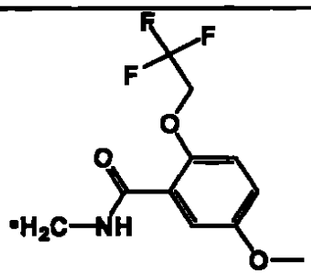
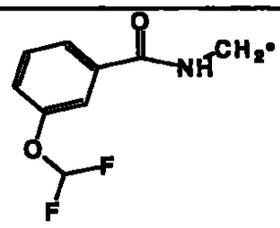
Ex.	R³ (• denotes link to structure)	Compound	LCMS ESI+ (M++)
85		4-[(3,5-Bis-trifluoromethyl-benzyl)-(3,5-dimethyl-isoxazol-4-ylmethyl)-carbamoyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	658
86		6,7-Dimethoxy-2-methyl-4-[(3,4,5-trifluoro-benzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	467
87		4-[(3,4-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	449
88		6,7-Dimethoxy-2-methyl-4-[(2,3,5-trifluoro-benzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	467
89		6,7-Dimethoxy-2-methyl-4-[(2,3,4,5,6-pentafluorobenzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	503
90		4-[(3-Fluoro-5-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499

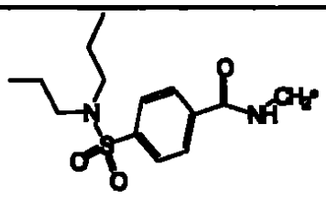
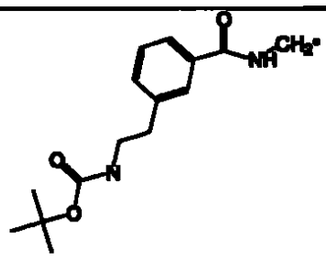
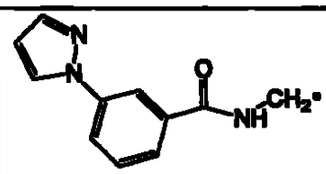
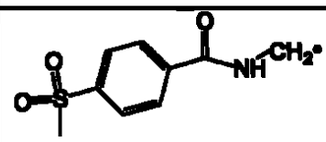
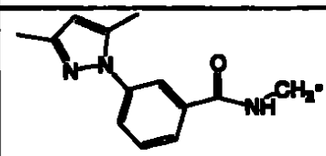
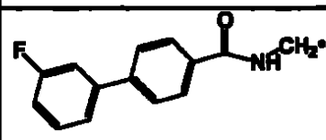
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
91		4-[(3-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499
92		4-[(5-Fluoro-2-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499
93		6,7-Dimethoxy-2-methyl-4-[(3-trifluoromethoxy-benzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	497
94		4-[[(4-Fluoro-naphthalene-1-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
95		6,7-Dimethoxy-2-methyl-4-[[(5-trifluoromethoxy-1H-indole-2-carbonyl)-amino]-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	536
96		4-[(2-Chloro-4-methanesulfonyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	525

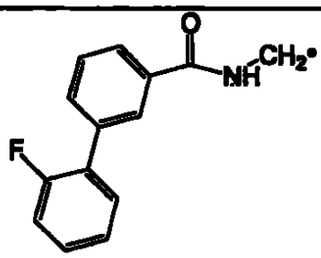
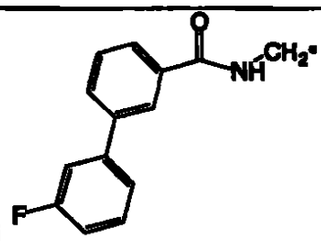
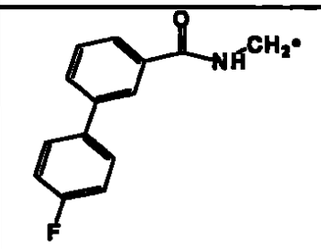
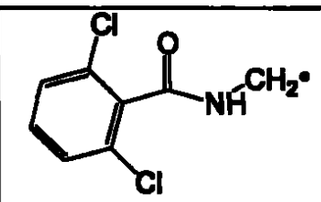
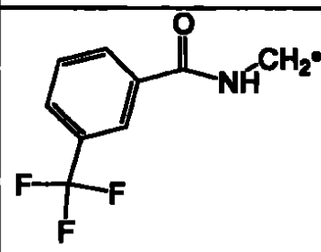
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
97		4-[(3-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499
96		4-[(2,4-Dimethoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	473
99		4-[(4-Fluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	431
100		6,7-Dimethoxy-2-methyl-4-[(2-trifluoromethyl-benzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	481
101		4-[(2-Chloro-4-fluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	465
102		6,7-Dimethoxy-2-methyl-4-[(4-trifluoromethoxy-benzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	497

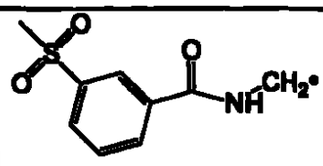
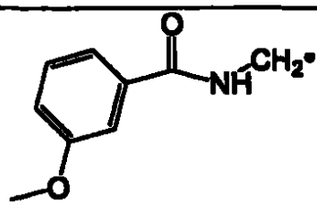
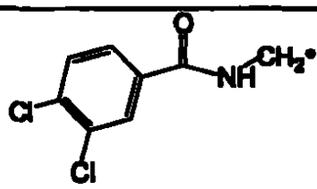
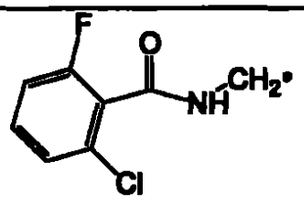
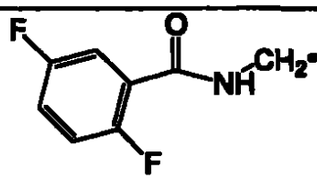
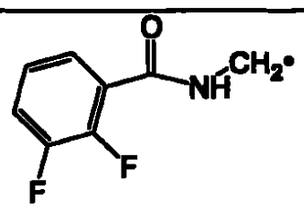
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
103		4-[(2-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499
104		6,7-Dimethoxy-2-methyl-4-[(2,3,6-trifluoro-benzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	467
105		4-[(2-Fluoro-3-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499
106		4-[(2-Chloro-4,5-difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	483
107		4-[(4-Fluoro-2-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499
108		4-[(4-Fluoro-3-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	499

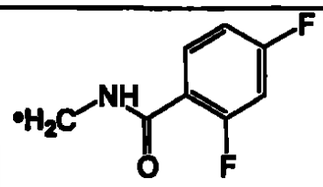
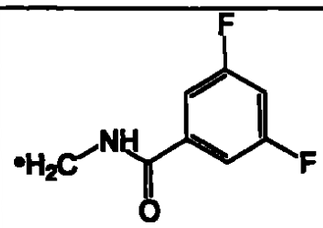
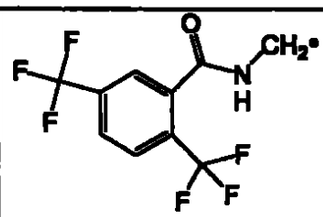
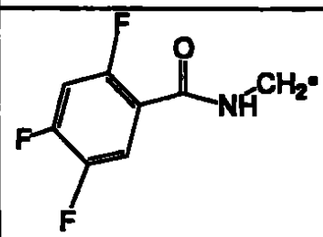
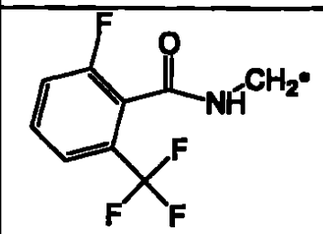
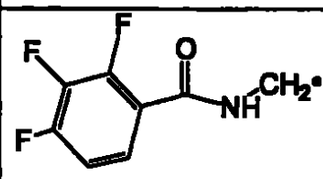
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
109		4-[(3,5-Dimethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	441
110		4-[(3-Fluoro-4-methyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	445
111		4-[(3-Fluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	431
112		6,7-Dimethoxy-4-[(3-methoxy-4-methyl-benzoylamino)-methyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	457
113		4-[(3-Chloro-2-fluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	465
114		6,7-Dimethoxy-2-methyl-4-[(2-trifluoromethoxy-benzoylamino)-methyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	497

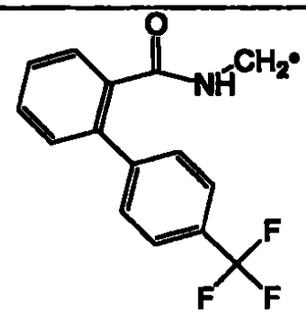
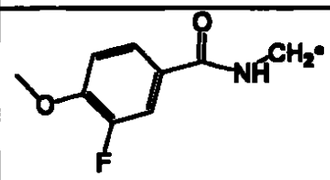
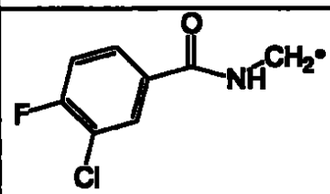
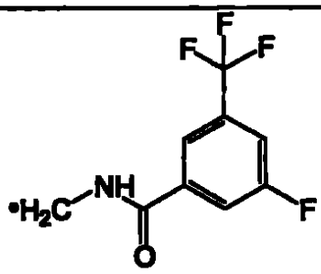
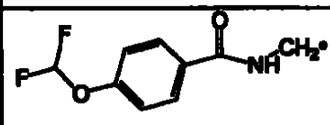
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
115		4-[(3-Ethoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	457
116		4-[(3-Chloro-4-methoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	477
117		4-[(3-Isopropoxy-4-methoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	501
118		6,7-Dimethoxy-4-{[5-methoxy-2-(2,2,2-trifluoro-ethoxy)-benzoylamino]-methyl}-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	541
119		4-[(3-Difluoromethoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	479

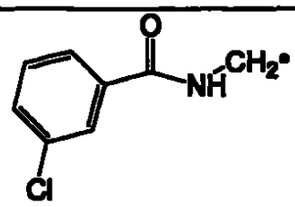
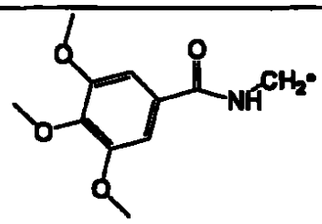
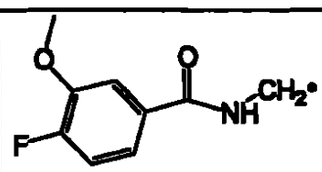
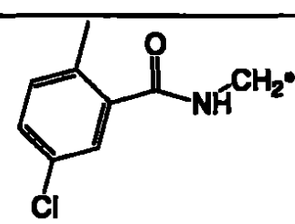
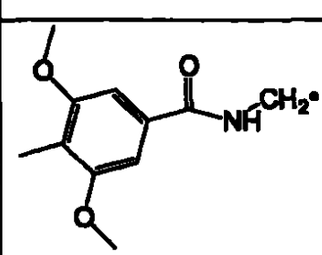
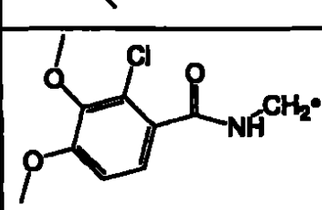
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
120		4-[(4-Dipropylsulfamoyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	576
121		4-[[3-(2-tert-Butoxycarbonylamino-ethyl)-benzoylamino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	556
122		6,7-Dimethoxy-2-methyl-4-[(3-pyrazol-1-yl-benzoylamino)-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	479
123		4-[(4-Methanesulfonyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	491
124		4-[[3-(3,5-Dimethyl-pyrazol-1-yl)-benzoylamino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	507
125		4-[[(3'-Fluoro-biphenyl-4-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	507

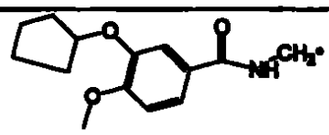
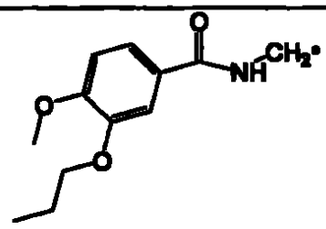
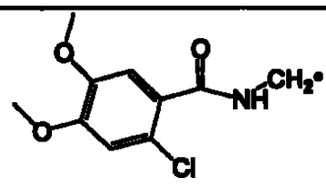
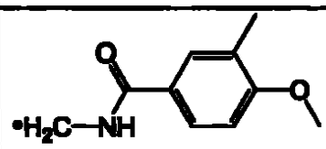
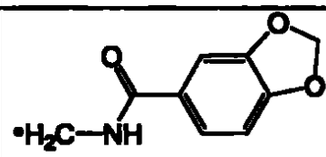
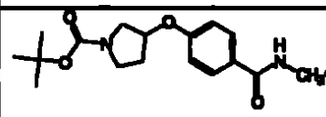
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
126		4-[[(2'-Fluoro-biphenyl-3-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	507
127		4-[[(3'-Fluoro-biphenyl-3-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	507
128		4-[[(4'-Fluoro-biphenyl-3-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	507
129		4-[(2,6-Dichloro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	481
130		6,7-Dimethoxy-2-methyl-4-[(3-trifluoromethyl-benzoylamino)-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	481

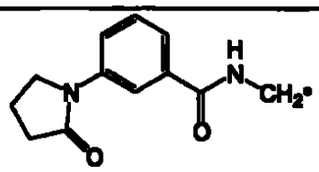
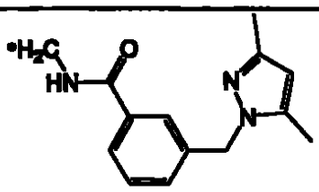
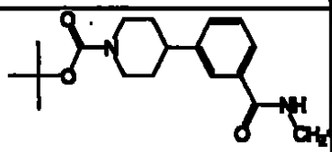
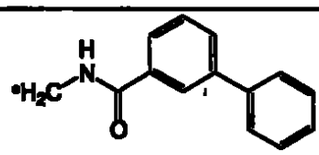
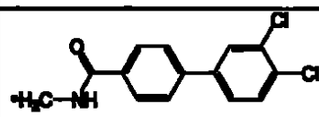
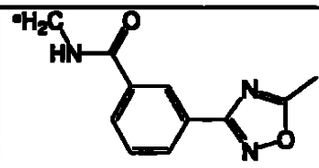
Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
131		4-[(3-Methanesulfonyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	491
132		6,7-Dimethoxy-4-[(3-methoxy-benzoylamino)-methyl]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	443
133		4-[(3,4-Dichloro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	481
134		4-[(2-Chloro-6-fluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	465
135		4-[(2,5-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	449
136		4-[(2,3-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	449

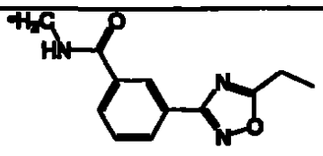
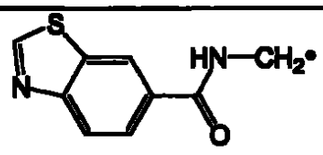
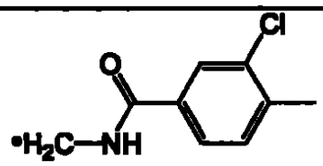
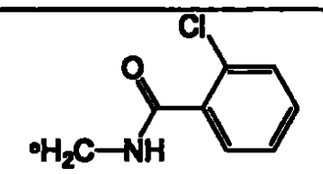
Ex.	R³ (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
137		4-[(2,4-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	449
138		4-[(3,5-Difluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	449
139		4-[(2,5-Bis-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	449
140		6,7-Dimethoxy-2-methyl-4-[(2,4,5-trifluoro-benzoylamino)-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	467
141		4-[(2-Fluoro-6-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	499
142		6,7-Dimethoxy-2-methyl-4-[(2,3,4-trifluoro-benzoylamino)-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	467

Ex.	R³ (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
143		6,7-Dimethoxy-2-methyl-4-[[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	557
144		4-[(3-Fluoro-4-methoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	461
145		4-[(3-Chloro-4-fluoro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	465
146		4-[(3-Fluoro-5-trifluoromethyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	499
147		4-[(4-Difluoromethoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	479

Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (M+H+)
148		4-[(3-Chloro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester	447
149		6,7-Dimethoxy-2-methyl-4-[(3,4,5-trimethoxy-benzoylamino)-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	503
150		4-[(4-Fluoro-3-methoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	461
151		4-[(5-Chloro-2-methyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	461
152		4-[(3,5-Dimethoxy-4-methyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	487
153		4-[(2-Chloro-3,4-dimethoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	507

Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
154		4-[(3-Cyclopentyloxy-4-methoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	527
155		6,7-Dimethoxy-4-[(4-methoxy-3-propoxy-benzoylamino)-methyl]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	501
158		4-[(2-Chloro-4,5-dimethoxy-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	507
157		6,7-Dimethoxy-4-[(4-methoxy-3-methyl-benzoylamino)-methyl]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	457
158		4-[[(Benzo[1,3]dioxole-5-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	457
159		4-[[4-(1-tert-Butoxycarbonyl-pyrrolidin-3-yloxy)-benzoylamino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl	498

Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
160		6,7-Dimethoxy-2-methyl-4-[[3-(2-oxo-pyrrolidin-1-yl)-benzoylamino]-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	496
161		4-[[3-(3,5-Dimethyl-pyrazol-1-ylmethyl)-benzoylamino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	521
162		4-[[3-(1-tert-Butoxycarbonyl-piperidin-4-yl)-benzoylamino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	496
163		4-[[(Biphenyl-3-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	489
164		4-[[(3',4'-Dichloro-biphenyl-4-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	557
165		6,7-Dimethoxy-2-methyl-4-[[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzoylamino]-methyl]-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	495

Ex.	R^3 (• denotes link to structure)	Compound	LCMS ESI+ (MH+)
166		4-[[3-(5-Ethyl-[1,2,4]oxadiazol-3-yl)-benzoylamino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	509
167		4-[[(Benzothiazole-6-carbonyl)-amino]-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	470
168		4-[(3-Chloro-4-methyl-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	461
169		4-[(2-Chloro-benzoylamino)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester	447

Preparation 34

3-Ethyl-6,7-dimethyl-3,4-dihydro-1H-quinoxalin-2-one

A mixture of 5,6-dimethyl phenylenediamine (22.45gm, 165mmol, 1eq), 2-ketobutyric acid (16.83gm, 165mmol, 1eq) and ethanol (75mL) were irradiated in the Milestone microwave (Milestone Laboratories, Sorisole, Italy) for 5 min at 180°C. The solid product upon cooling was filtered and washed with ethanol. Concentration of the filtrate and further crystallization provided the desired quinoxalin-2-one (18.45gm, 55.2%).

^{1}H-NMR (dmso-d6): δ 1.17 (t, J=7.05Hz, 3H), 2.25 (s, 3H), 2.28 (s, 3H), 2.74 (q, J=7.05Hz, 2H), 7.00 (s, 1H), 7.48 (s, 1H), 12.15 (brs, 1H).

ESI-MS: 203 (MH+).

Preparation 35

3-Chloro-2-ethyl-6,7-dimethyl-1,2-dihydro-quinoxaline

3-Ethyl-6,7-dimethyl-3,4-dihydro-1H-quinoxalin-2-one (18.45g, 91.2mmol) was dissolved in 180mL phosphorus oxychloride and the mixture was heated overnight at 110°C under a drying tube charged with potassium hydroxide and Drierite®. After cooling, the phosphorus (V) oxychloride was carefully distilled off, and residue was carefully quenched with ice, followed by saturated sodium hydrogen carbonate. The aqueous suspension was extracted several times with methylene chloride. The combined organics were washed 1 time with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give the title compound (19.3gm, 81%), which was carried forward without further purification.

^{1}H-NMR (dmso-d6): δ 1.30 (t, J=7.47Hz, 3H), 3.04 (q, J=7.47Hz, 2H), 7.74, (s, 1H), 7.83 (s, 1H).

Preparation 36

2-Ethyl-6,7-dimethyl-1,2,3,4-tetrahydro-quinoxaline

The residue containing 3-chloro-2-ethyl-6,7-dimethyl-1,2-dihydro-quinoxaline was dissolved in 200mL acetic acid and 18.2g sodium acetate was added (222mmol, 3eq). After flushing with nitrogen, the vessel was charged with palladium on carbon (10%, 7.88gm, 0.1eq Pd, 7.39mmol). The reaction was subjected to hydrogenation at 45psi for 5 hr whereupon hydrogen uptake ceased. The reaction was filtered through Celite® and evaporated. The residue was azeotroped 3 times with heptane to remove further acetic acid. The residue was then partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic layer was washed 3 times with saturated aqueous sodium hydrogen carbonate, 1 time with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Flash chromatography eluting with a 20-50% ethyl acetate /hexanes gradient provided the desired quinoxaline (10.56gm, 83% yield.) as a fluffy pinkish solid.

^{1}H-NMR (dmso-d6): δ 0.89 (t, J=7.46Hz, 3H), 1.35 (m, 2H), 1.89, (s, 3H), 1.94 (s, 3H), 2.75 (m, 1H), 2.96 (m, 1H), 3.14 (m, 1H), 6.12, (s, 1H), 6.17 (s, 1H).

Preparation 37

3-Ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid tert-butyl ester

2-Ethyl-6,7-dimethyl-1,2,3,4-tetrahydro-quinoxaline (10.56g, 55.6mmol, 1eq) was dissolved in anhydrous methylene chloride and cooled to -30°C in an ethylene glycol/dry ice bath. A solution of di-tert-butyl dicarbonate (12.13gm, 55.6mmol, 1eq) in methylene chloride (50mL) was added dropwise, and the reaction was allowed to slowly warm to room temperature overnight. The reaction was evaporated to dryness and repartitioned between ethyl acetate and 0.1M HCl. The organic layer was washed 3 times with 0.1M HCl, 1 time with saturated sodium hydrogen carbonate, 1 time with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Silica chromatography eluting with 10% ethyl acetate /hexane provided the desired compound (10.35g, 64%).

^{1}H-NMR (dmso-d6): δ 0.90 (t, J=7.47Hz, 3H), 1.34 (m, 2H), 1.41 (s, 9H), 2.02 (s, 6H), 3.09 (m, 1H), 3.24 (m, 1H), 3.58 (m, 1H), 5.74 (s, 1H), 6.34 (s, 1H), 7.05 (brs, 1H).

ESI-MS: 290 (M+), 235 (MH+ - isobutylene).

Preparation 38

2-Ethyl-6,7-dimethyl-2,3-dihydro-quinoxaline-1,4-dicarboxylic acid 4-tert-butyl ester 1-ethyl ester

A solution of 3-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid tert-butyl ester (10.35gm, 35.7mmol, 1eq) and 4-dimethylaminopyridine (436mg, 3.57mmol , 0.1eq) in anhydrous pyridine (250mL) was cooled to 0°C and ethyl chloroformate (17.0mL, 178.3mmol, 5eq) was added dropwise. The reaction was allowed to warm to room temperature overnight. The solvents were evaporated under vacuum and azeotroped 3 times with heptanes. The residue, after drying under vacuum, was partitioned between ethyl acetate and 0.1M HCl. The organic layer was extracted with 0.1M HCl until the extracts were acidic, then was washed 1 time with saturated aqueous sodium hydrogen carbonate, 1 time with water, 1 time with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to provide the desired compound (100%).

^{1}H-NMR (dmso-d6): δ 0.77 (t, J=7.05Hz, 3H), 1.20 (t, J=7.05Hz, 3H), 1.25 (m, 2H), 1.44 (s, 9H), 2.13 (s, 6H), 3.55 (dd, J=13.35, 4.98Hz, 1H), 3.78 (dd, J=13.1, 3.32Hz, 1H), 4.12 (m, 2H), 4.39 (m, 1H), 7.41 (s, 1H), 7.44 (s, 1H).

ESI-MS: 307 (MH+-isobutylene), 263 (MH+ - boc).

Preparation 39

2-Ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester:

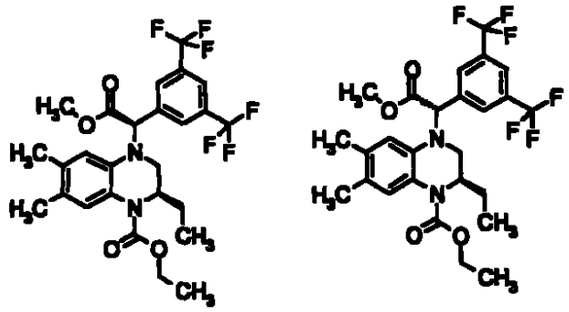
To 2-Ethyl-6,7-dimethyl-2,3-dihydro-quinoxaline-1,4-dicarboxylic acid 4-tert-butyl ester 1-ethyl ester (12.93g) was added trifluoroacetic acid (200mL), the mixture was stirred until a solution had formed and then evaporated to dryness under vacuum. The residue was azeotroped 3 times with heptane and dried under vacuum. The residual oil was then partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The aqueous layer was extracted 3 times with methylene chloride. The combined methylene chloride extracts were dried over anhydrous sodium sulfate, filtered and evaporated, giving the desired quinoxaline (100%).

^{1}H-NMR (dmso-d6): δ 0.77 (t, J=7.47Hz, 3H), 1.19 (t, J=7.05Hz, 3H), 1.24 (m, 2H), 2.02 (s, 6H), 3.14 (m, 2H), 4.08 (m, 2H), 4.24 (m, 1H), 5.72 (m, 1H), 7.11 (brs, 1H).

ESI-MS: 263 (MH+).

This racemic quinoxaline was subjected to preparative chiral separations using a ChiralcelOD 10x25cm chiral preparative column. The eluent was 5% ethanol in heptane, at a flow rate of 275mL/min, observing at 300nm. The sample was loaded on the column using 2:1 methanol/dichloromethane. Retention time of the S-enantiomer was 16min, the R-enantiomer was 22min. A 25g sample was subjected to these conditions, resulting in 10g of the R-enantiomer, 99.4%ee, and 11g of the S-enantiomer, 95.1%ee.

Examples 170, 171, 172 and 173



(*R,R*, *R,S*, *S,R* and *S,S*) -4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

Method A: A mixture of (*RS*)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (652mg, 1eq, 2.5mmol), bromo-4-(3,5-bis-trifluoromethyl-phenyl)-acetic acid methyl ester (1.0gm, 1.1eq, 2.74mmol) and 2,6-lutidine (0.87mL, 3eq, 7.47mmol) in dimethylformamide (3mL) were heated at 140°C for 20 min by microwave irradiation in an Emrys Optimizer (Personal Chemistry, Uppsala, Sweden). The mixture was partitioned between methylene chloride and water, and the phases were separated. The aqueous phase was extracted 3 times with methylene chloride, and the combined organic extracts were washed 2 times with water, 1 time with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Chromatography on silica gel using 10% ethyl acetate in hexanes as eluant provided the title compounds as a mixture of two diastereoisomers (900mg, 66%).

Method B: A mixture of (*RS*)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (652mg, 1eq, 2.5mmol), bromo-4-(3,5-bis-trifluoromethyl-phenyl)-acetic acid methyl ester (1.0gm, 1.1eq, 2.74mmol) and 2,6-lutidine (0.87mL, 3eq, 7.47mmol) in dimethylformamide (3mL) were stirred at room temperature for 24

hours. The mixture was partitioned between methylene chloride and water, and the phases were separated. The aqueous phase was extracted 3 times with methylene chloride, and the combined organic extracts were washed 2 times with water, 1 time with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Chromatography on silica gel using 10% ethyl acetate in hexanes as eluant provided the title compounds as a mixture of two diastereoisomers (900mg, 66%).

Diastereoisomer 1 ^{1}H-NMR ($CDCl_3$): δ 0.71 (t, J=7.57Hz, 3H), 1.30 (t, J=7.05Hz, 3H), 1.46 (m, 2H), 2.18 (s, 3H), 2.20 (s, 3H), 2.77 (dd, J=9.54, 2.08Hz,1H), 3.37 (dd, J=11.38, 3.32Hz, 1H) 3.82 (s, 3H), 4.20 (m, 2H), 4.26 (m, 1H), 5.82 (s, 1H), 6.58 (s,1H), 7.49 (brs, 1H) 7.75 (s,2H), 7.88 (s,1H).

LCMS (ESI+): 547 (MH+)

Diastereoisomer 2: ^{1}H-NMR ($CDCl_3$): δ 0.87 (t, J=7.47Hz, 3H), 1.28 (t, J=6.64Hz, 3H), 1.43 (m, 2H), 2.18 (s, 3H), 3.11 (dd, J=11.35, 4.98Hz, 1H), 3.22 (dd, J=10.79, 1.66Hz, 1H), 3.83 (s, 3H), 4.19 (m, 2H), 4.44 (m, 1H), 5.66 (s, 1H), 6.41 (s, 1H), 7.28 (brs, 1H), 7.73 (s, 2H), 7.86 (s, 1H).

LCMS (ESI+): 547 (MH+).

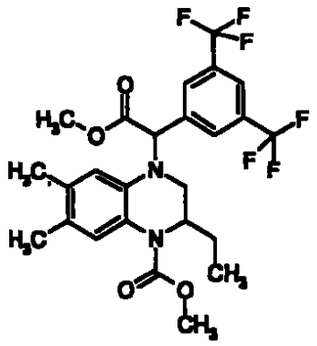
This racemic mixture of diastereoisomers could be further resolved by chiral HPLC on a Pirkle Covalent (S,S)Whelk-O 1 column (Regis Technologies, Inc., Morton Grove, IL) (5 x 25cm) eluting at 100mL/min with 5% ethanol/heptane to provide three fractions:

Isomer 1, Retention time=18min

Isomers 2 and 3, Retention time=25min

Isomer 4, Retention time=37min

Examples 174 and 175



Preparation of 4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester

This compound was prepared using the procedure as described above for 4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester, but using methyl chloroformate in the place of ethyl chloroformate.

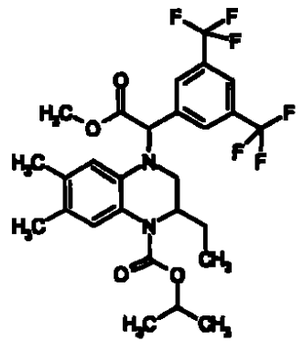
Diastereoisomer 1 ^{1}H-NMR ($CDCl_3$): δ 0.86 (t, J=7.47Hz, 3H), 1.43 (m, 2H), 2.18 (s, 6H), 3.10 (dd, J=11.48, 4.98Hz, 1H), 3.22 (dd, J=11.17Hz 1.66Hz, 1H), 3.75 (s, 3H), 4.43 (m, 1H), 3.82 (s, 3H), 5.86 (s, 1H), 6.41 (s, 1H), 7.22 (brs, 1H), 7.72 (s, 2H), 7.86 (s, 1H).

LCMS (ESI+): 532 (M+).

Diastereoisomer 2 ^{1}H-NMR ($CDCl_3$): δ 0.71 (t, J=7.47Hz, 3H), 1.19 (m, 1H), 1.43 (m, 1H), 2.19 (s, 3H), 2.20 (s, 3H), 2.77 (dd, J=11.47, 1.65Hz, 1H), 3.38 (dd, J=11.30, 3.74Hz, 1H), 3.77 (s, 3H), 3.81 (s, 3H), 4.38 (m, 1H), 5.83 (s, 1H), 6.58 (s, 1H), 7.37 (s, 1H), 7.75 (s, 2H), 7.88 (s, 1H).

LCMS (ESI+): 532 (M+).

Examples 176 and 177



Preparation of 4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester

This compound was prepared using the procedure as described above for compound 4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester, but using isopropyl chloroformate in the place of ethyl chloroformate.

Diastereoisomer 1 ^{1}H-NMR ($CDCl_3$): δ 0.86 (t, J=7.47Hz, 3H), 1.16 (dd, J=6.22, 6.22Hz, 3H), 1.26 (dd, J=15.07, 6.22Hz, 3H), 1.50 (m, 2H), 2.17, (s, 6H), 3.10, (m, 1H), 3.2 (m, 1H), 3.82 (s, 3H), 4.42 (m, 1H), 5.00 (m, 1H), 5.85 (s, 1H), 6.40 (s, 1H), 7.31 (brs, 1H), 7.64 (s, 1H), 7.74 (s, 1H).).

LCMS (ESI+): 560 (M+).

Diastereoisomer 2 ^{1}H-NMR ($CDCl_3$): δ 0.71 (t, J=7.47, 3H), 1.16 (m, 1H), 1.26 (d, J=6.23Hz), 1.29 (d, J=5.81Hz), 1.44 (m, 1H), 2.16 (s, 3H), 2.20 (s, 3H), 2.76 (dd, J=11.52, 2.07Hz, 1H), 3.37 (dd, J=11.52, 3.32Hz), 3.82 (s, 3H), 4.38 (m, 1H), 5.01 (m, 1H), 5.82 (s, 1H), 6.58 (s, 1H), 7.47 (brs, 1H), 7.75 (s, 2H), 7.88 (s, 1H).

LCMS (ESI+): 561 (MH+).

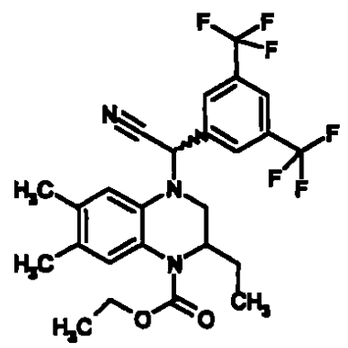
Preparation 40

(3,5-Bis-trifluoromethyl-phenyl)-bromo-acetonitrile

To a solution of (3,5-bis-trifluoromethyl-phenyl)-acetonitrile (2.0g, 7.9mmol) in carbon tetrachloride (20mL) was added dibenzoyl peroxide (0,076g, 0.3mmol) and N-bromosuccinnimide (1.4g, 7.9mmol). This reaction mixture was refluxed for 24h then diluted with methylene chloride and washed with brine. The organic layer was dried and concentrated to afford the crude product which was purified by silica gel chromatography using 2% ethyl acetate in hexanes as eluant to afford the title compound (2.0g, 75%).

LCMS (ESI+): 333 (MH+).

Example 178



4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

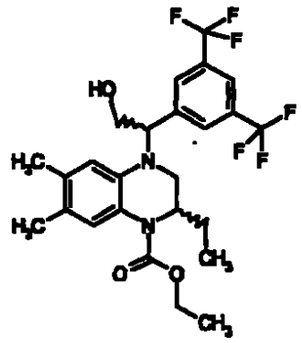
Method A: A mixture of 2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (1g, 1eq, 3.81mmol), 3,5-bis-(trifluoromethyl-phenyl)-bromo-acetonitrile (Preparation 40, 1.27gm, 1eq, 3.81mmol) and potassium carbonate (1.58gm, 3eq, 11.43mmol) in acetonitrile (5mL) was subjected to microwave irradiation in the Emrys Optimizer (Personal Chemistry, Uppsala, Sweden) at 140°C for 20 min. The reaction was partitioned between ethyl acetate and water, and the phases were separated. The aqueous phase was extracted 3 times with ethyl acetate, and the combined organic extracts were washed 2 times with water, 1 time

with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Chromatography on silica gel using a gradient of 10-30% ethyl acetate in hexanes as eluant provided the desired nitrile as a mixture of two diastereoisomers (1.5:1)(900mg, 29%).

Method B: A mixture of 2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (1g, 1eq, 3.81mmol), 3,5-bis-(trifluoromethyl-phenyl)-bromo-acetonitrile (Preparation 40, 1.27gm, 1eq, 3.81mmol) and 2,6-lutidine (3eq, 11.43mmol) in N,N-dimethylformamide (5mL) was stirred at room temperature for 24 hours. The reaction was partitioned between ethyl acetate and water, and the phases were separated. The aqueous phase was extracted 3 times with ethyl acetate, and the combined organic extracts were washed 2 times with water, 1 time with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Chromatography on silica gel using a gradient of 10-30% ethyl acetate in hexanes as eluant provided the desired nitrile as a mixture of two diastereoisomers (1.5:1)(900mg, 29%).

LCMS (ESI+): 514 (MH+)

Example 179



Preparation of 4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

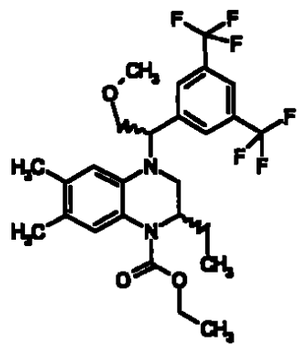
To a solution of the 4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (0.14g, 0.26mmol) in tetrahydrofuran (5mL) at –78°C was added a solution of lithium aluminum hydride (1M in tetrahydrofuran, 0.16mL) dropwise. This solution was slowly warmed to room temperature over 3 h. The reaction mixture was quenched with sodium sulfate hexahydrate (2gm) and the mixture was stirred for 30 min. The reaction mixture was filtered and concentrated to afford the crude product (mixture of

diastereoisomers) which was purified by silica gel chromatography eluting with 10% ethyl acetate in hexanes to give the title compound (0.08g, 70%).

^{1}H-NMR ($CDCl_3$): δ 0.71 (t, J=7.57Hz, 3H), 0.95 (t, J=7.05Hz, 3H), 1.28 (m, 2H), 2.20 (bs, 6H), 2.97 (dd, 1H), 3.25 (m, 1H), 3.37 (m, 1H), 3.85 (m, 2H), 4.15 (m, 3H), 4.5 (bm, 1H), 4.62(m, 1H), 4.70 (m, 1H), 5.82 (s, 1H), 6.58 (s, 1H), 7.49 (brs, 1H) 7.75 (s, 2H), 7.88 (s, 1H).

LCMS (ESI+): 518 (MH+)

Example 180



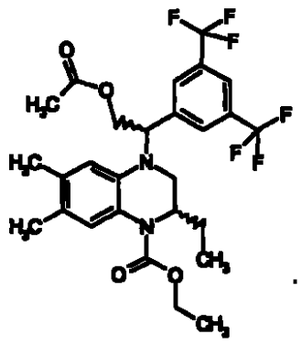
Preparation of 4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-methoxy-ethyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

To a solution of 4-[1-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (0.044gm, 0.13mmol) in anhydrous dimethylformamide (93mL), was added sodium hydride (60% suspension, 0.005gm, 0.27mmol) and the mixture was stirred for 20 min. Excess of methyl iodide was added and the reaction was stirred for 1h and quenched with saturated ammonium chloride. The mixture was extracted with ether (3x20mL) and concentrated. Silica gel chromatography of the crude product using a gradient of 10-30% ethyl acetate in hexanes as eluant provided the desired product as an oil (0.015gm, 35%).

^{1}H-NMR ($CDCl_3$): δ 0.71 (t, J=7.57Hz, 3H), 1.30 (t, J=7.05Hz, 3H), 1.46 (m, 2H), 2.20 (brs, 6H), 2.97 (dd, 1H), 3.25 (m, 1H), 3.37 (m, 1H), 3.4 (s, 3H), 3.85 (m, 2H), 4.26 (m, 1H), 4.5 (bm, 1H), 4.62(m, 1H), 4.70 (m, 1H), 5.82 (s, 1H), 6.58 (s, 1H), 7.49 (brs, 1H), 7.75 (s,2H), 7.88 (s,1H).

LCMS (ESI+): 532 (MH+).

Example 181



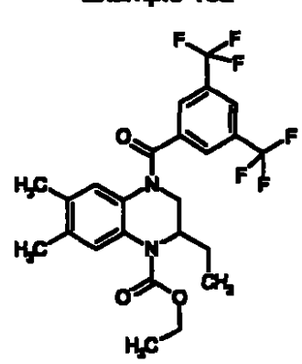
Preparation of 4-[2-Acetoxy-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester was dissolved in a 1:1 mixture of acetic anhydride and pyridine (4mL) and the mixture was stirred at ambient temperature for 10h. The solvent was removed in vacuo and the residue was purified by silica gel chromatography to afford the desired acetate (25 mg, 58%; mixture of diastereoisomers)

^{1}H-NMR ($CDCl_3$): δ 0.71 (t, J=7.57Hz, 3H), 1.30 (t, J=7.05Hz, 3H), 1.46 (m, 2H), 1.98 (s, 3H) 2.16 (s, 3H), 2.20 (s, 3H), 2.77 (dd, 1H), 3.05 (m, 1H), 3.37 (m, 1H), 4.20 (m, 2H), 4.26 (m, 1H), 4.5 (m, 1H), 4.82(m, 1H), 4.70 (m, 1H), 5.82 (s, 1H), 6.58 (s, 1H), 7.49 (brs, 1H), 7.75 (s,2H), 7.88 (s,1H).

LCMS (ESI+): 560 (MH+)

Example 182



Preparation of 4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

A room-temperature solution of 2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (0.1gm, 1eq, 0.38mmol) in 5mL methylene chloride was treated with the acid chloride formed by combination of 3,5-bis-(trifluoromethyl)benzoic acid (147mg, 1.5eq, 0.57mmol), oxalyl chloride (0.05mL, 1.5eq, 0.57mmol) and a drop of anhydrous dimethylformamide. The reaction was allowed to stir overnight at room temperature, at which time the reaction was quenched with saturated sodium hydrogen carbonate and extracted 3 times with methylene chloride. The combined organic extracts were washed 1 time with 1M HCl, 1 time with saturated sodium hydrogen carbonate, 1 time with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Chromatography on silica gel using a 10-20% ethyl acetate in hexanes gradient provided 4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (130mg, 68%).

^{1}H-NMR ($CDCl_3$): δ 0.91 (t, J=7.47Hz, 3H), 1.30 (t, J=7.04Hz, 3H), 1.50 (m, 1H), 1.60 (m, 1H), 1.94 (s, 3H), 2.20 (s, 3H), 3.39 (m, 1H), 4.26 (q, J=6.22Hz, 2H), 4.68 (m, 2H), 6.29 (brs, 1H), 7.41 (brs, 1H), 7.78 (s, 2H), 7.85 (s, 1H).

FIA-MS (APCI+): 503 (MH+).

Preparation 41

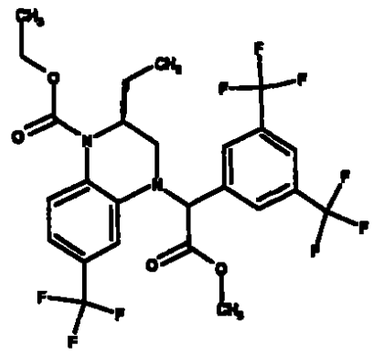
6-Trifluoromethyl-1,2,3,4-tetrahydro-quinoxaline

This desired quinoxaline was prepared using the method described by V. Krchnak *et.al.* (*Tetrahedron Lett.* 42, 2443-2446 (2001)), using 3-(*R*)-amino-pentan-1-ol and 2-fluoro-5-trifluoromethyl-nitrobenzene.

^{1}H-NMR (dmso-d6): δ 1.06 (t, J=7.48Hz, 3H), 1.73 (m, J=7.90Hz, 2H), 3.19 (dd, J=9.96Hz, 1H), 3.68 (dd, J=9.55Hz, 1H), 3.71 (m, 1H), 6.98 (d, J=8.3Hz, 1H), 7.25 (dd, 1H), 7.43 (s, 1H).

ESI-MS: 231 (MH+).

Example 183



4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

A solution of 6-trifluoromethyl-1,2,3,4-tetrahydro-quinoxaline (Preparation 41, .01g, 0.04mmol, 1eq), 3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl bromide (0.017g, 0.044mmol, 1.1eq), and 2,6-lutidine (.014g, 0.12mmol 3eq) in dimethylformamide (0.5mL) were irradiated in the Milestone microwave (Milestone Laboratories, Sorisole, Italy) for 10 min at 140°C. The solvent was removed under reduced pressure to yield a dark oil which was used without further purification.

ESI-MS: 542 (MH^+).

This residue was combined with 2,6-lutidine (0.018g, 0.16mmol, 2eq) and ethyl chloroformate (0.0175g, 0.16mmol, 2eq) in dimethylformamide (0.5mL) and heated at 140°C for 10 min by irradiation in a Milestone microwave (Milestone Laboratories, Sorisole, Italy). The solution was purified by preparative HPLC eluting with water 0.1%NH_4OH, 70 – 0% with acetonitrile, 0.1%NH_4OH, 6min gradient time, and8min run time to yield the title compound.

ESI-MS: 587 (MH+)

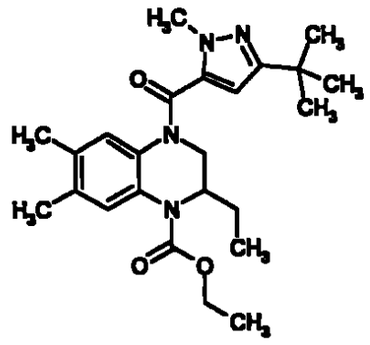
General procedure for parallel synthesis of amides:

The required benzoic acids (0.06mmol, 1eq) were combined with PS-PPh_3 (115mg, 1.51mmol/g, 3eq, 0.18mmol) (Argonaut Technologies, Inc., Foster City, CA) in septum-capped 2 dram vials. To this solid mixture was added dichloroethane (1mL) *via* a Tecan US (Research Triangle Park, NC) liquid handler. To this suspension was added *via* the Tecan a solution of trichloroacetonitrile (0.0072mL, 1.2eq, 0.07mmol) in dichloroethane (1mL) and the reactions were gently agitated by means of an orbital shaker for 3h. To this solution was added PS-DIPAM (56mg,

3.2mmol/g, 3eq, 0.18mmol)(Polymer Laboratories, Amherst, MA) and a solution of 2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (15mg, 0.06mmol, 1.0eq) in dichloroethane (1mL) was added *via* the Tecan. The reactions were agitated overnight. The reactions were filtered through filter tubes using the Tecan liquid handler, and the resins were washed 3 times with dichloroethane. The solutions were evaporated using a Genevac Mega660 centrifugal evaporator (Genevac Ltd.. Suffolk, UK) and the residues were redissolved in dimethyl sulfoxide (0.2mL) and purified using the Shimadzu preparative HPLC system (Shimadzu Corporation, Kyoto, Japan) eluting with a 30-100% acetonitrile/water/0.1% formic acid gradient on a 19x50mm Waters Symmetry Column (Waters Corp, Milford, MA) 8 min run, 6 min gradient, 25mL/min, UV triggered collection, observing at 210nm. The product-containing fractions were evaporated to dryness using the Genevac Mega660 centrifugal evaporator (Genevac Ltd., Suffolk, UK).

Using the appropriate starting materials, Examples 184-409 were made as racemic mixtures in an analogous manner to Example 183:

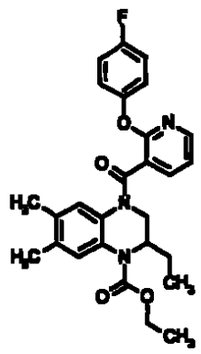
Example 184



4-(5-tert-Butyl-2-methyl-2H-pyrazole-3-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

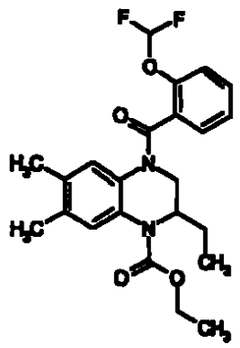
Example 185



2-Ethyl-4-[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): (MH+).

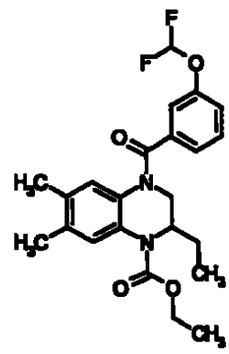
Example 186



4-(2-Difluoromethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 478 (MH+).

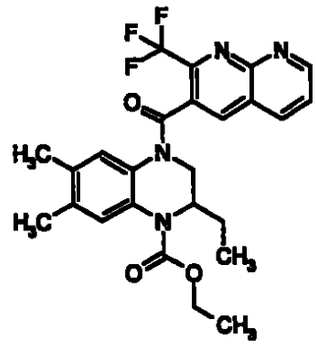
Example 187



4-(3-Difluoromethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 433 (MH+).

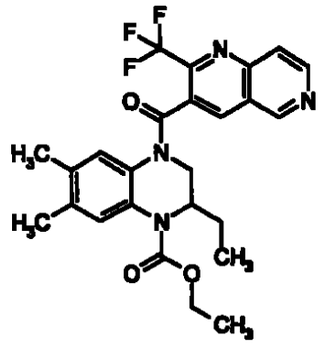
Example 188



2-Ethyl-6,7-dimethyl-4-(2-trifluoromethyl-[1,8]naphthyridine-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 487 (MH+).

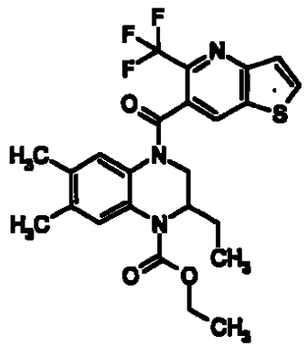
Example 189



2-Ethyl-6,7-dimethyl-4-(2-trifluoromethyl-[1,6]naphthyridine-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 487 (MH+).

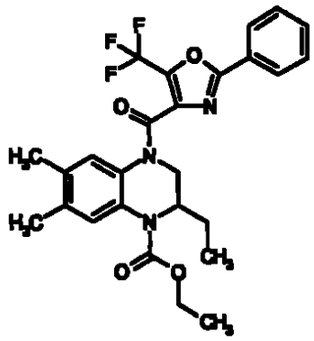
Example 190



2-Ethyl-6,7-dimethyl-4-(5-trifluoromethyl-thieno[3,2-b]pyridine-6- carbonyl)-3,4-dihydro-2H-quinoxaline-1- carboxylic acid ethyl ester

LC-MS (ESI+): 492 (MH+).

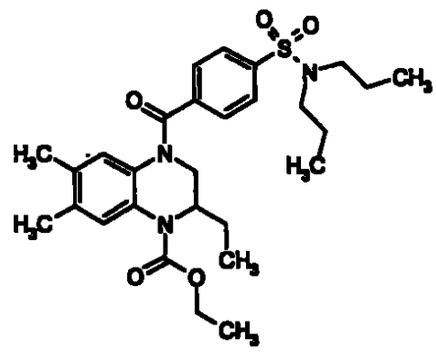
Example 191



2-Ethyl-6,7-dimethyl-4-(2-phenyl-5-trifluoromethyl-oxazole-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 502 (MH+).

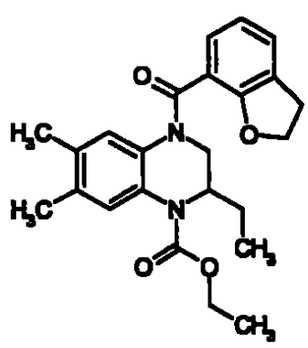
Example 192



4-(4-Dipropylsulfamoyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 530 (MH+).

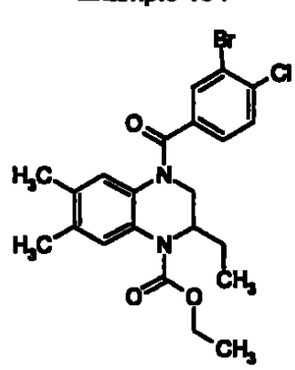
Example 193



4-(2,3-Dihydro-benzofuran-7-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 409 (MH+).

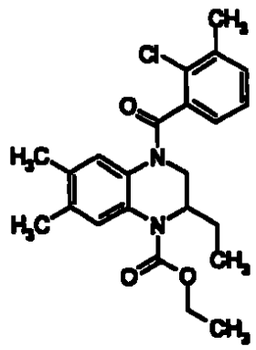
Example 194



4-(3-Bromo-4-chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 480 (MH+).

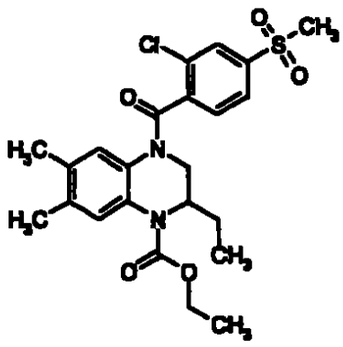
Example 195



4-(2-Chloro-3-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 415 (MH+).

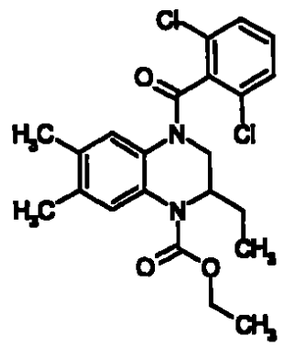
Example 196



4-(2-Chloro-4-methanesulfonyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 479 (MH+).

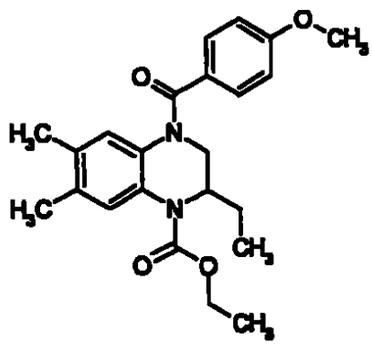
Example 197



4-(2,6-Dichloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 436 (MH+).

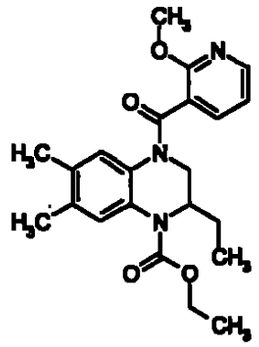
Example 198



2-Ethyl-4-(4-methoxy-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 397 (MH+).

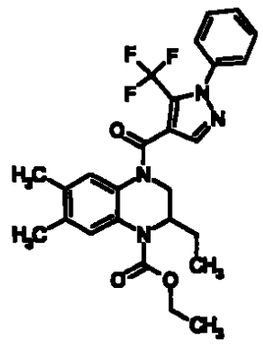
Example 199



2-Ethyl-4-(2-methoxy-pyridine-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 398 (MH+).

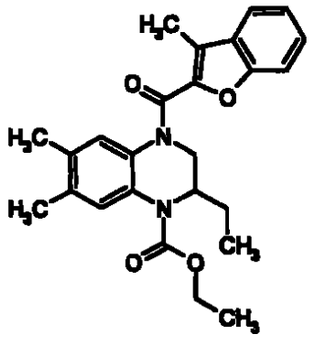
Example 200



2-Ethyl-6,7-dimethyl-4-(1-phenyl-5-trifluoromethyl-1H-pyrazole-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 501 (MH+).

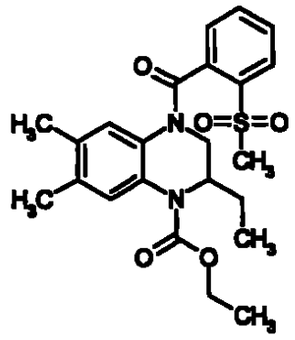
Example 201



2-Ethyl-6,7-dimethyl-4-(3-methyl-benzofuran-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 421(MH+).

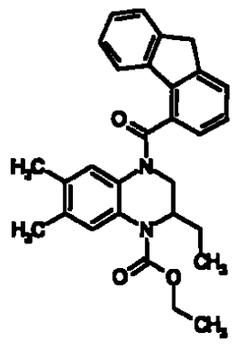
Example 202



2-Ethyl-4-(2-methanesulfonyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 445 (MH+).

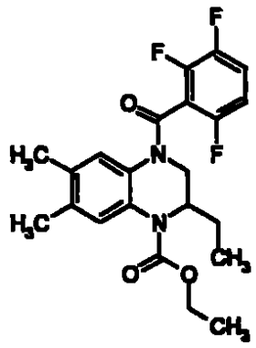
Example 203



2-Ethyl-4-(9H-fluorene-4-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 455 (MH+).

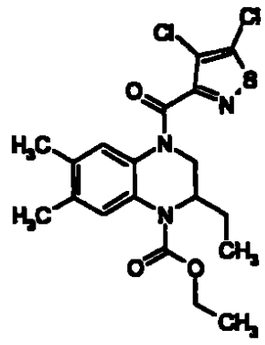
Example 204



2-Ethyl-6,7-dimethyl-4-(2,3,6-trifluoro-benzoyl)-3,4-dihydro-2H- quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 421 (MH+).

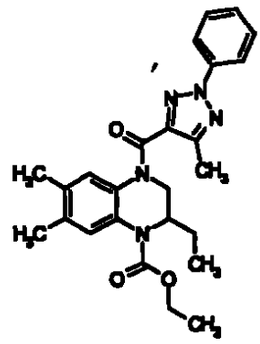
Example 205



4-(4,5-Dichloro-isothiazole-3-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 443 (MH+).

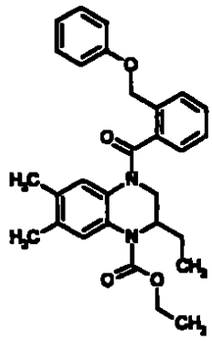
Example 206



2-Ethyl-6,7-dimethyl-4-(5-methyl-2-phenyl-2H[1,2,3]triazole-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 448 (MH+).

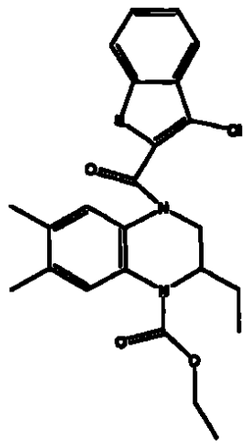
Example 207



2-Ethyl-6,7-dimethyl-4-(2-phenoxymethyl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 473 (MH+).

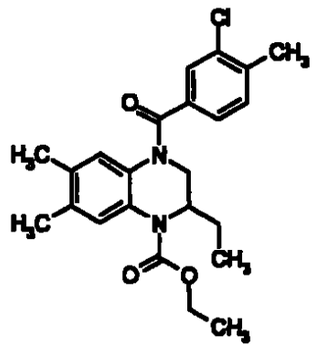
Example 208



4-(3-Chloro-benzo[b]thiophene-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 457 (MH+).

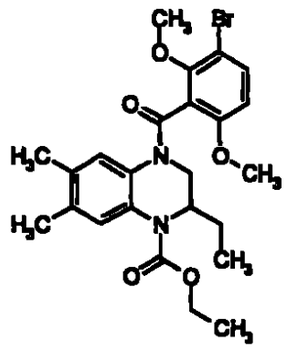
Example 209



4-(3-Chloro-4-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 415 (MH+).

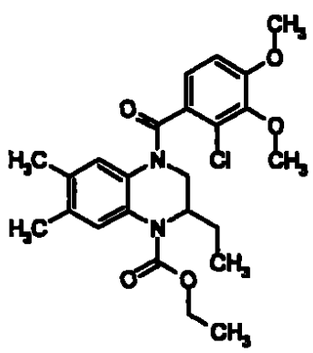
Example 210



4-(3-Bromo-2,6-dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro- 2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 506 (MH+).

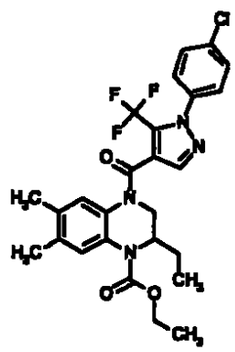
Example 211



4-(2-Chloro-3,4-dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 461 (MH+).

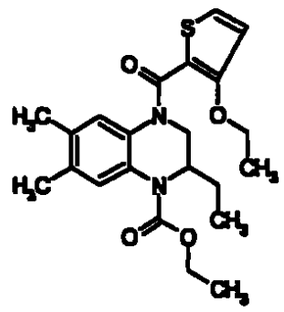
Example 212



4-[1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carbonyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 535 (MH+).

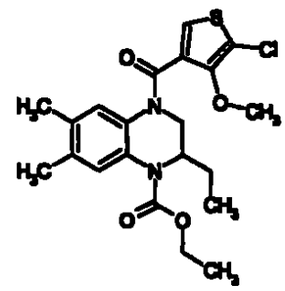
Example 213



4-(3-Ethoxy-thiophene-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 417 (MH+).

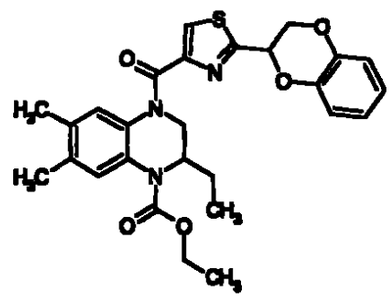
Example 214



4-(5-Chloro-4-methoxy-thiophene-3-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 437 (MH+).

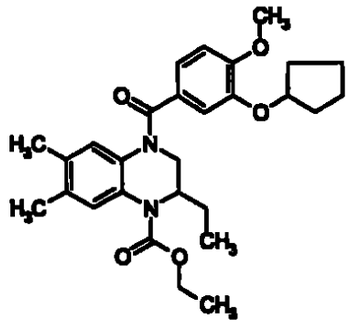
Example 215



4-[2-(2,3-Dihydro-benzo[1,4]dioxin-2-yl)-thiazole-4-carbonyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 508 (MH+).

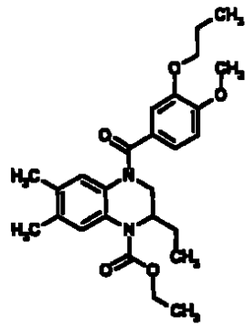
Example 216



4-(3-Cyclopentyloxy-4-methoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 481 (MH+).

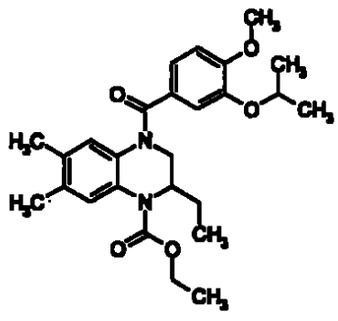
Example 217



2-Ethyl-4-(4-methoxy-3-propoxy-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 455 (MH+).

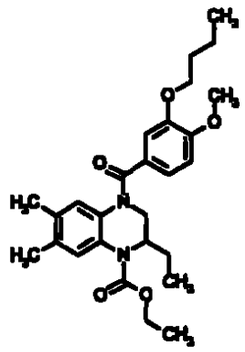
Example 218



2-Ethyl-4-(3-isopropoxy-4-methoxy-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 455 (MH+).

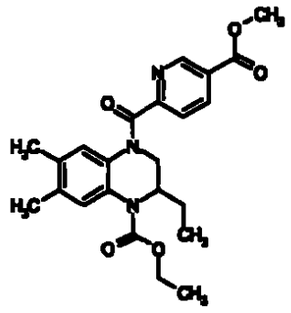
Example 219



4-(3-Butoxy-4-methoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 469 (MH+).

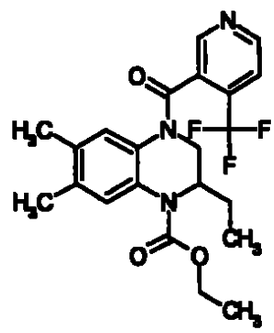
Example 220



2-Ethyl-4-(5-methoxycarbonyl-pyridine-2-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 426 (MH+).

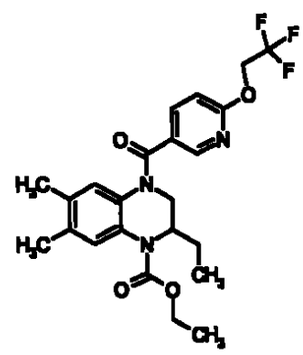
Example 221



2-Ethyl-6,7-dimethyl-4-(4-trifluoromethyl-pyridine-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 436 (MH+).

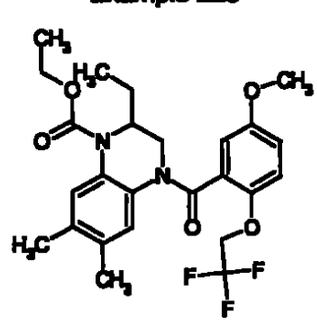
Example 222



2-Ethyl-6,7-dimethyl-4-[6-(2,2,2-trifluoro-ethoxy)-pyridine-3-carbonyl]-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):466 (MH+).

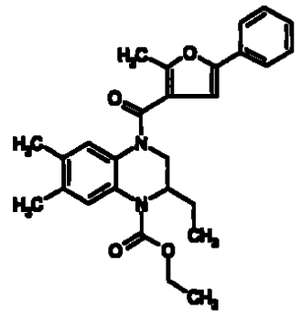
Example 223



2-Ethyl-4-[5-methoxy-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):495 (MH+).

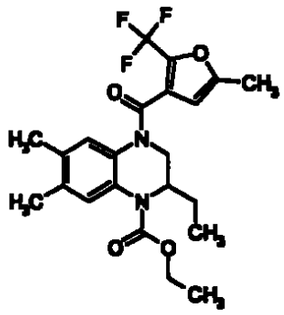
Example 224



2-Ethyl-6,7-dimethyl-4-(2-methyl-5-phenyl-furan-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 447 (MH+).

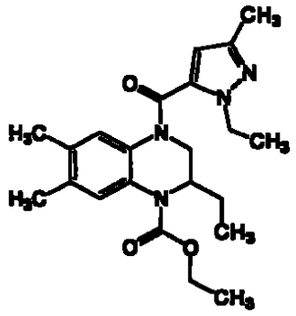
Example 225



2-Ethyl-6,7-dimethyl-4-(5-methyl-2-trifluoromethyl-furan-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 439 (MH+).

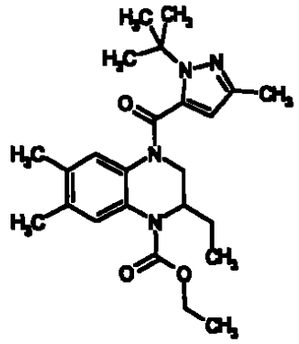
Example 226



2-Ethyl-4-(2-ethyl-5-methyl-2H-pyrazole-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 399 (MH+).

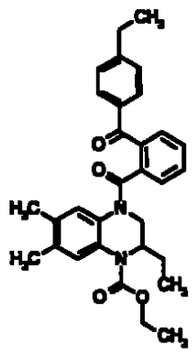
Example 227



4-(2-tert-Butyl-5-methyl-2H-pyrazole-3-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

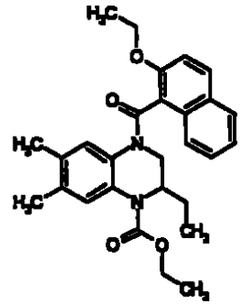
Example 228



2-Ethyl-4-[2-(4-ethyl-benzoyl)-benzoyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 499 (MH+).

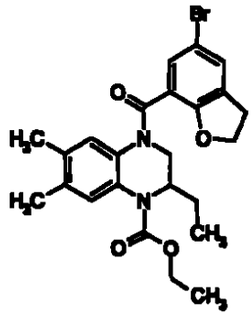
Example 229



4-(2-Ethoxy-naphthalene-1-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 461 (MH+).

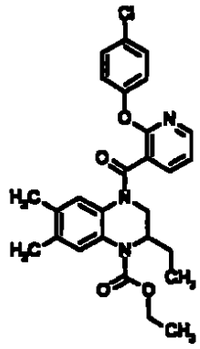
Example 230



4-(5-Bromo-2,3-dihydro-benzofuran-7-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 488 (MH+).

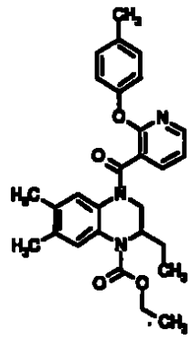
Example 231



4-[2-(4-Chloro-phenoxy)-pyridine-3-carbonyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 494 (MH+).

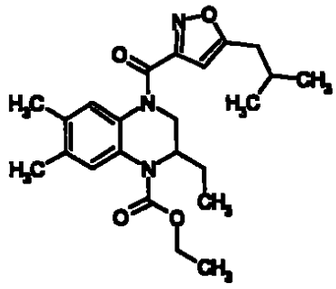
Example 232



2-Ethyl-6,7-dimethyl-4-(2-p-tolyloxy-pyridine-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 474 (MH+).

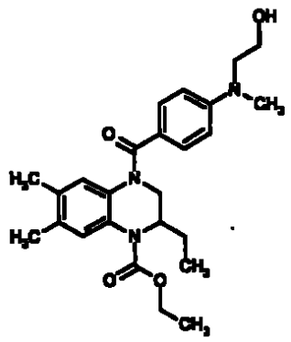
Example 233



2-Ethyl-4-(5-isobutyl-isoxazole-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):414 (MH+).

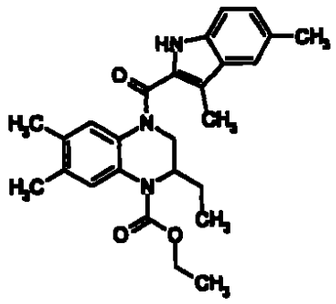
Example 234



2-Ethyl-4-[4-[(2-hydroxy-ethyl)-methyl-amino]-benzoyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 440 (MH+).

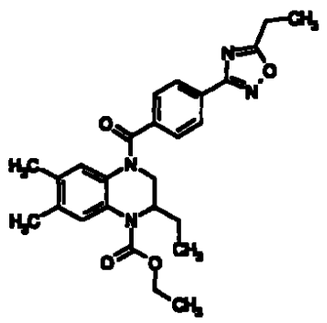
Example 235



4-(3,5-Dimethyl-1H-indole-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 434 (MH+).

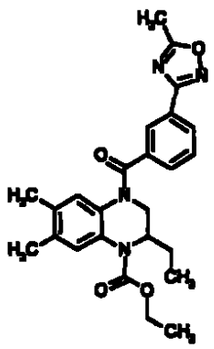
Example 236



2-Ethyl-4-[4-(5-ethyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 463 (MH+).

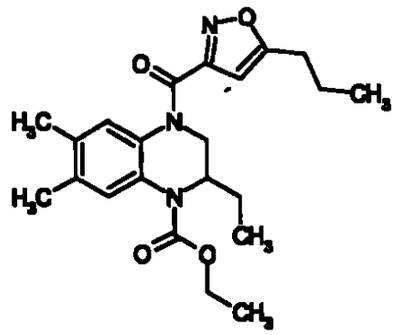
Example 237



2-Ethyl-6,7-dimethyl-4-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 449 (MH+).

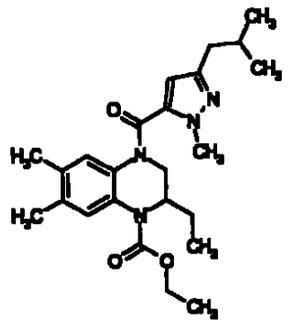
Example 238



2-Ethyl-6,7-dimethyl-4-(5-propyl-isoxazole-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+)400 (MH+).

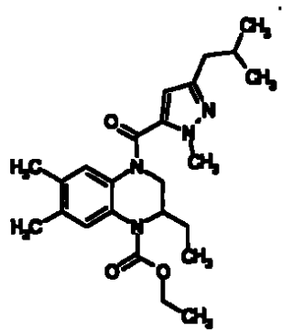
Example 239



2-Ethyl-4-(5-isobutyl-2-methyl-2H-pyrazole-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

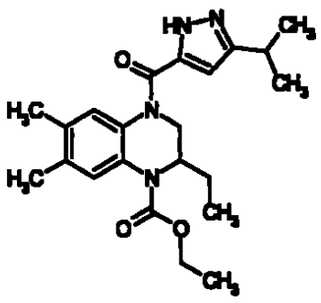
Example 240



2-Ethyl-4-(5-methoxymethyl-furan-2-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 401 (MH+).

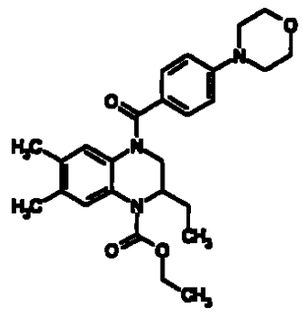
Example 241



2-Ethyl-4-(5-isopropyl-2H-pyrazole-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 399 (MH+).

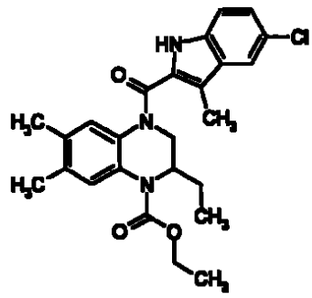
Example 242



2-Ethyl-6,7-dimethyl-4-(4-morpholin-4-yl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 452 (MH+).

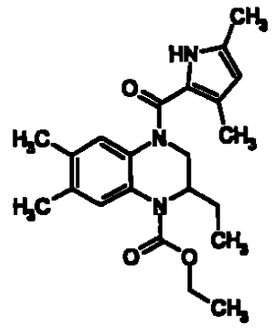
Example 243



4-(5-Chloro-3-methyl-1H-indole-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 454 (MH+).

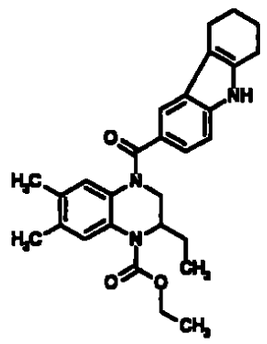
Example 244



4-(3,5-Dimethyl-1H-pyrrole-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 384 (MH+).

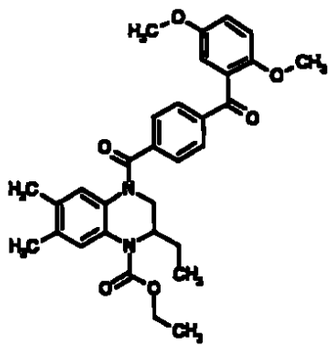
Example 245



2-Ethyl-6,7-dimethyl-4-(6,7,8,9-tetrahydro-5H-carbazole-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

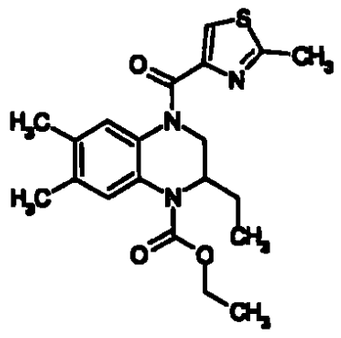
Example 246



4-[4-(2,5-Dimethoxy-benzoyl)-benzoyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 531 (MH+).

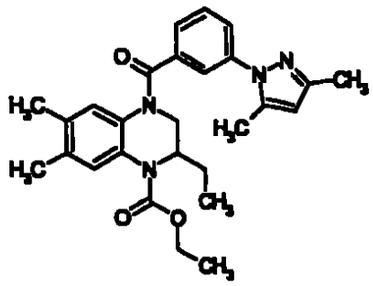
Example 247



2-Ethyl-6,7-dimethyl-4-(2-methyl-thiazole-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):388 (MH+).

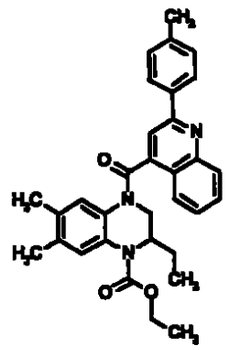
Example 248



4-[3-(3,5-Dimethyl-pyrazol-1-yl)-benzoyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 461 (MH+).

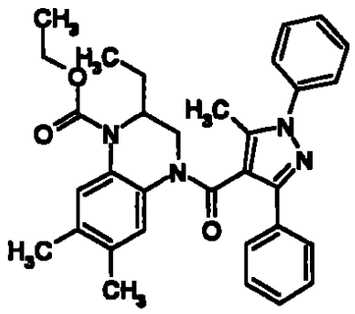
Example 249



2-Ethyl-6,7-dimethyl-4-(2-p-tolyl-quinoline-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 508 (MH+).

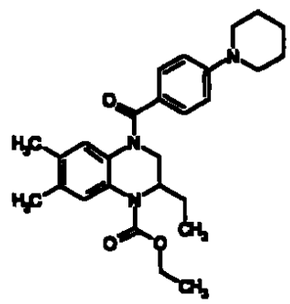
Example 250



2-Ethyl-6,7-dimethyl-4-(5-methyl-1,3-diphenyl-1H-pyrazole-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 523 (MH+).

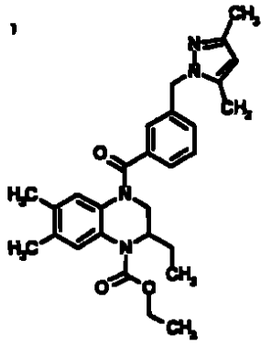
Example 251



2 -Ethyl-6,7-dimethyl-4-(4-piperidin-1-yl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 450 (MH+).

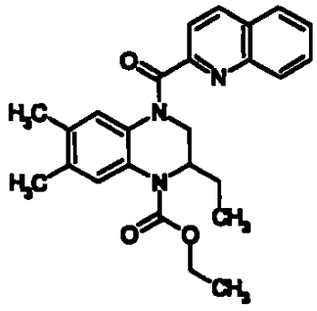
Example 252



4-[3-(3,5-Dimethyl-pyrazol-1-ylmethyl)-benzoyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 475 (MH+).

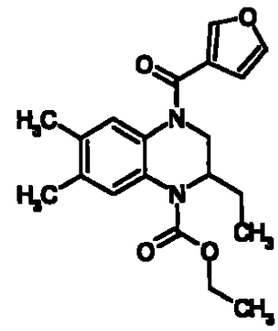
Example 253



2-Ethyl-6,7-dimethyl-4-(quinoline-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 418 (MH+).

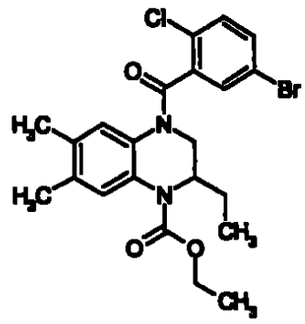
Example 254



2-Ethyl-4-(furan-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 357 (MH+).

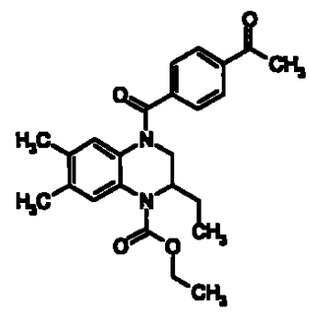
Example 255



4-(5-Bromo-2-chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 480 (MH+).

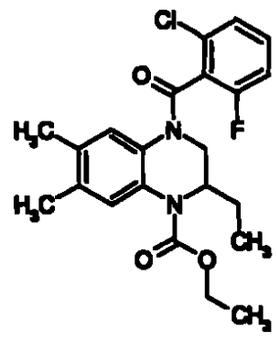
Example 256



4-(4-Acetyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 409 (MH+).

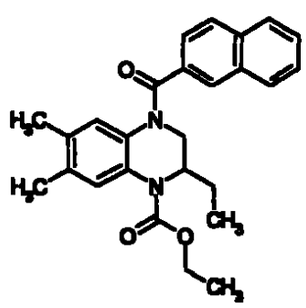
Example 257



4-(2-Chloro-6-fluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 419 (MH+).

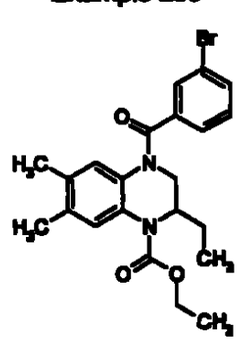
Example 258



2-Ethyl-6,7-dimethyl-4-(naphthalene-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 417 (MH+).

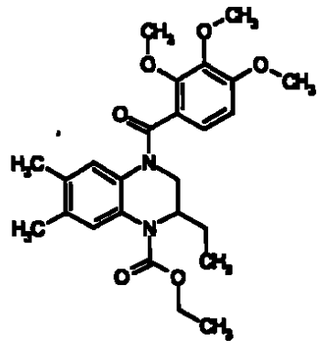
Example 259



4-(3-Bromo-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 446 (MH+).

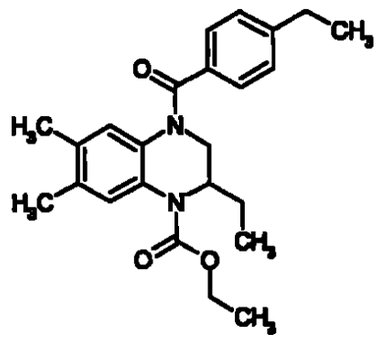
Example 260



2-Ethyl-6,7-dimethyl-4-(2,3,4-trimethoxy-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 457 (MH+).

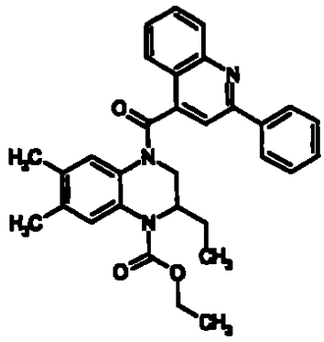
Example 261



2-Ethyl-4-(4-ethyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):395 (MH+).

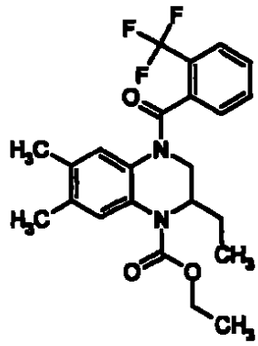
Example 262



2-Ethyl-6,7-dimethyl-4-(2-phenyl-quinoline-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 494 (MH+).

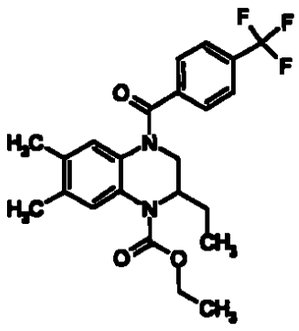
Example 283



2-Ethyl-6,7-dimethyl-4-(2-trifluoromethyl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 435 (MH+).

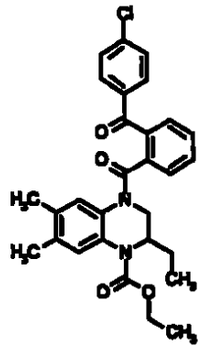
Example 284



2-Ethyl-6,7-dimethyl-4-(4-trifluoromethyl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 435 (MH+).

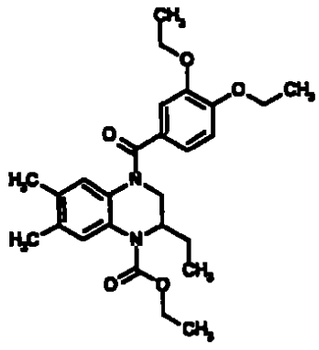
Example 265



4-[2-(4-Chloro-benzoyl)-benzoyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 506 (MH+).

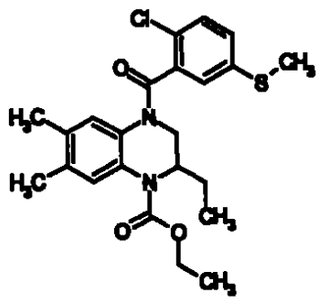
Example 266



4-(3,4-Diethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 455 (MH+).

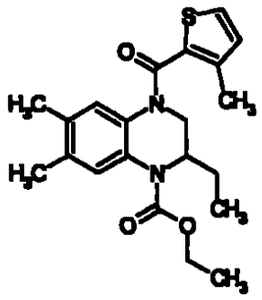
Example 267



4-(2-Chloro-5-methylsulfanyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 448 (MH+).

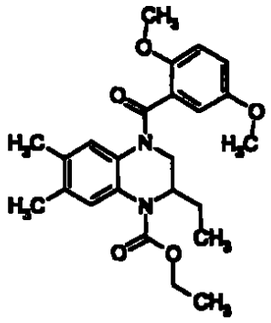
Example 268



2-Ethyl-6,7-dimethyl-4-(3-methyl-thiophene-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 387 (MH+).

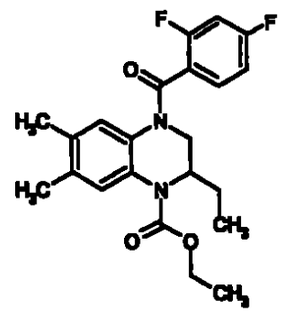
Example 269



4-(2,5-Dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

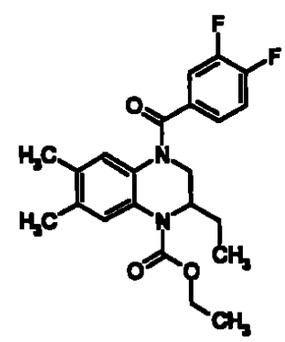
Example 270



4-(2,4-Difluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 403 (MH+).

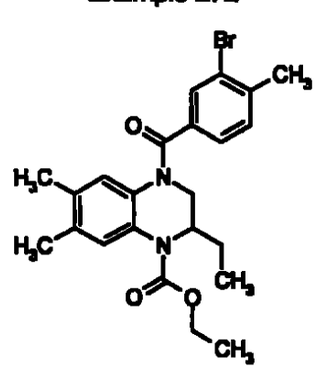
Example 271



4-(3,4-Difluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):403 (MH+).

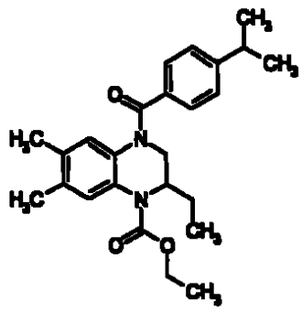
Example 272



4-(3-Bromo-4-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

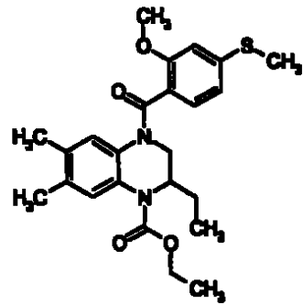
Example 273



2-Ethyl-4-(4-isopropyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 409 (MH+).

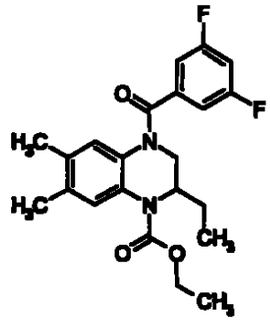
Example 274



2-Ethyl-4-(2-methoxy-4-methylsulfanyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):443 (MH+).

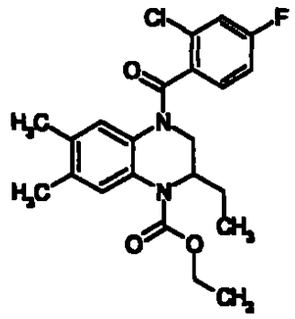
Example 275



4-(3,5-Difluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 403 (MH+).

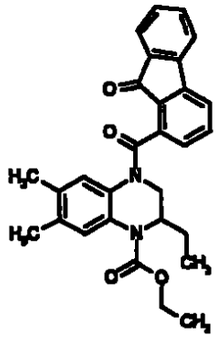
Example 276



4-(2-Chloro-4-fluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):419 (MH+).

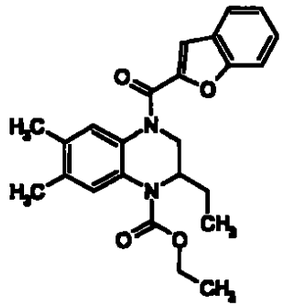
Example 277



2-Ethyl-6,7-dimethyl-4-(9-oxo-9H-fluorene-1-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 469 (MH+).

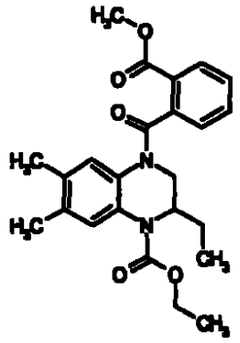
Example 278



4-(Benzofuran-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 407 (MH+).

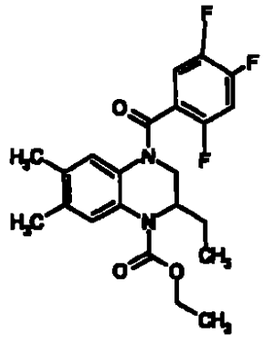
Example 279



2-Ethyl-4-(2-methoxycarbonyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 425 (MH+).

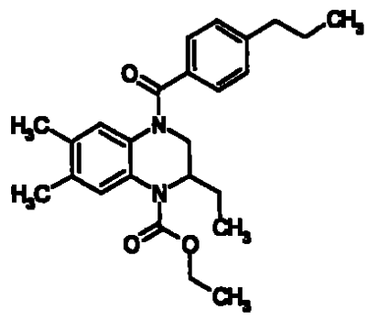
Example 280



2-Ethyl-6,7-dimethyl-4-(2,4,5-trifluoro-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 421 (MH+).

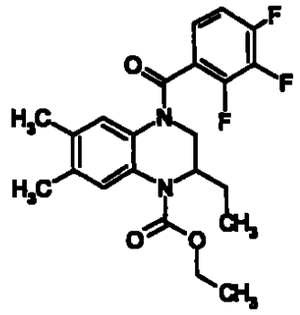
Example 281



2-Ethyl-6,7-dimethyl-4-(4-propyl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 409 (MH+).

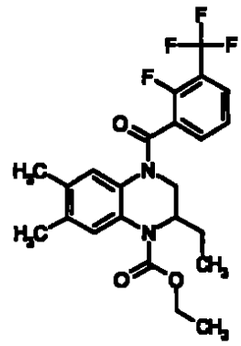
Example 282



2-Ethyl-6,7-dimethyl-4-(2,3,4-trifluoro-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 421 (MH+).

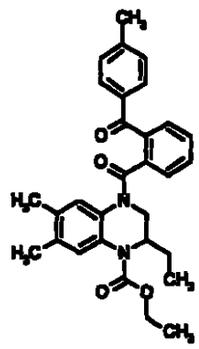
Example 283



2-Ethyl-4-(2-fluoro-3-trifluoromethyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 453 (MH+).

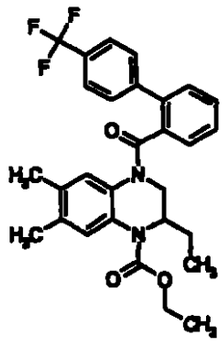
Example 284



2-Ethyl-6,7-dimethyl-4-[2-(4-methyl-benzoyl)-benzoyl]-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 485 (MH+).

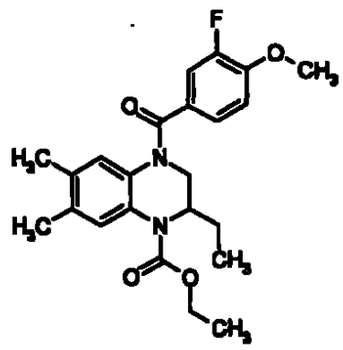
Example 285



2-Ethyl-6,7-dimethyl-4-(4'-trifluoromethyl-biphenyl-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):511 (MH+).

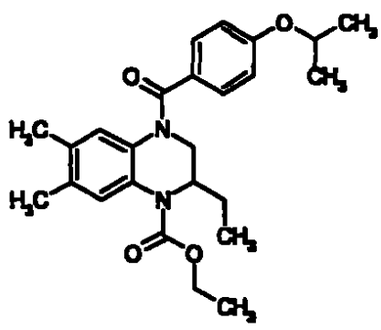
Example 286



2-Ethyl-4-(3-fluoro-4-methoxy-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):415 (MH+).

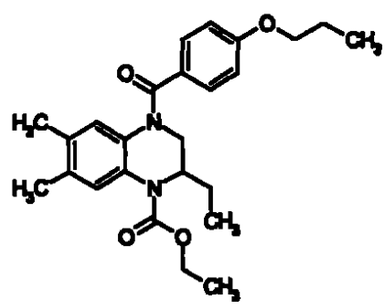
Example 287



2-Ethyl-4-(4-isopropoxy-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 425 (MH+).

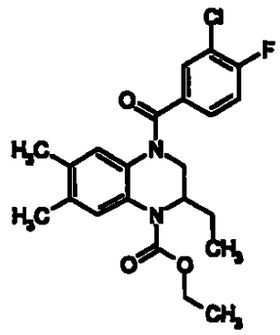
Example 288



2-Ethyl-6,7-dimethyl-4-(4-propoxy-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 425 (MH+).

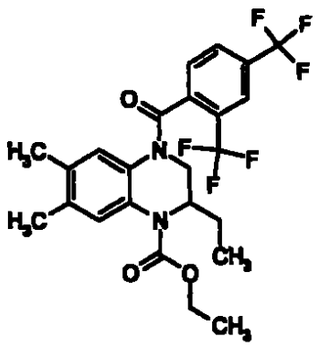
Example 289



4-(3-Chloro-4-fluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):419 (MH+).

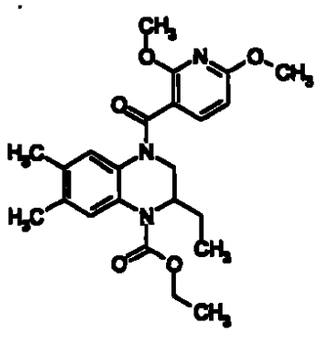
Example 290



4-(2,4-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 503 (MH+).

Example 291

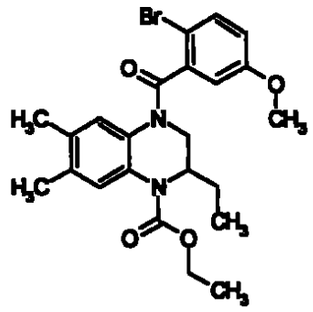


4-(2,6-Dimethoxy-pyridine-3-carbonyl)-2-ethyl

-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 428 (MH+).

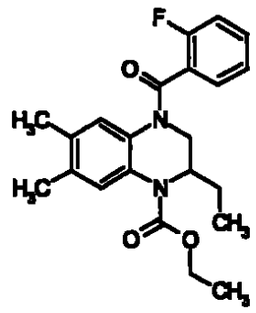
Example 292



4-(2-Bromo-5-methoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 476 (MH+).

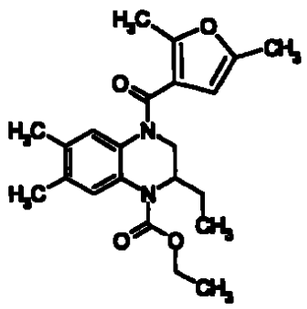
Example 293



2-Ethyl-4-(2-fluoro-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 385 (MH+).

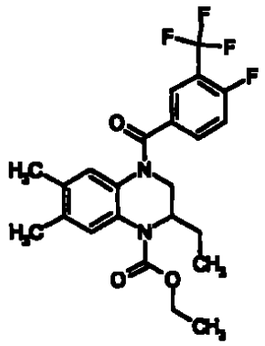
Example 294



4-(2,5-Dimethyl-furan-3-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 385 (MH+).

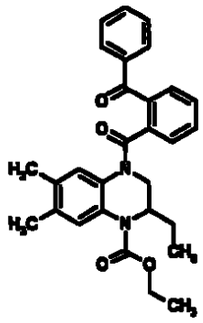
Example 295



2-Ethyl-4-(4-fluoro-3-trifluoromethyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 453 (MH+).

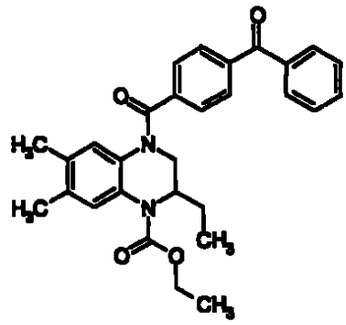
Example 296



4-(2-Benzoyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 471 (MH+).

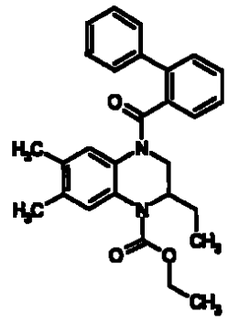
Example 297



4-(4-Benzoyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 471 (MH+).

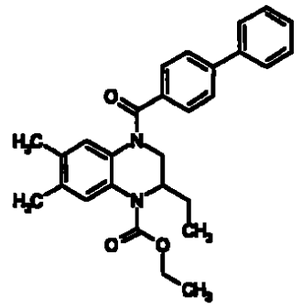
Example 298



4-(Biphenyl-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 443 (MH+).

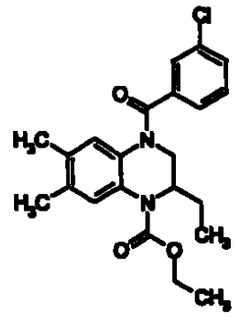
Example 299



4-(Biphenyl-4-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 443 (MH+).

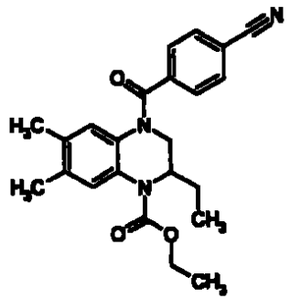
Example 300



4-(3-Chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):401 (MH+).

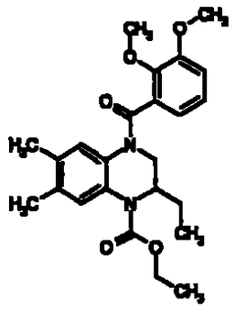
Example 301



4-(4-Cyano-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):392 (MH+).

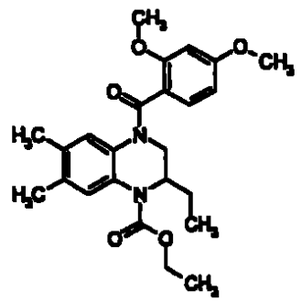
Example 302



4-(2,3-Dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

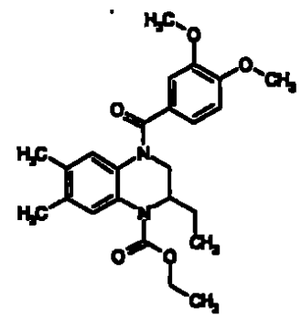
Example 303



4-(2,4-Dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):427 (MH+).

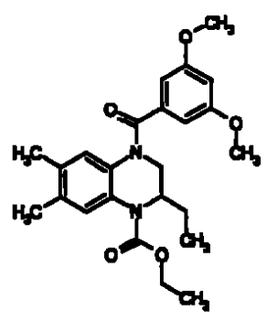
Example 304



4-(3,4-Dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

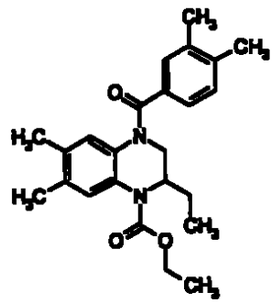
Example 305



4-(3,5-Dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

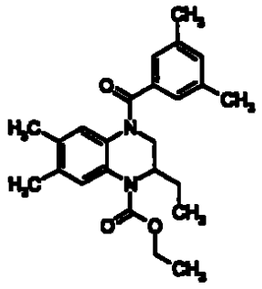
Example 306



4-(3,4-Dimethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):395 (MH+).

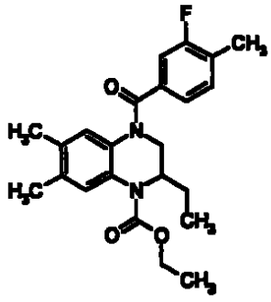
Example 307



4-(3,5-Dimethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 395 (MH+).

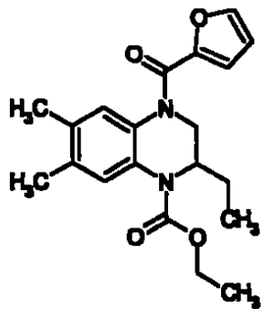
Example 308



2-Ethyl-4-(3-fluoro-4-methyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 399 (MH+).

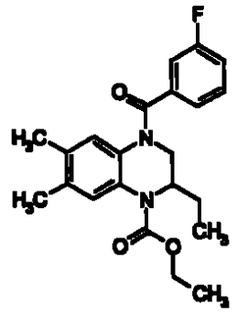
Example 309



2-Ethyl-4-(furan-2-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 357 (MH+).

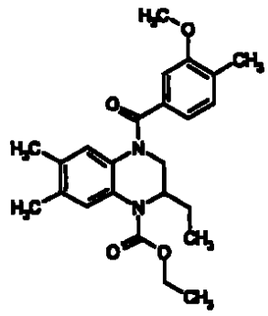
Example 310



2-Ethyl-4-(3-fluoro-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline- 1-carboxylic acid ethyl ester

LC-MS (ESI+): 385 (MH+).

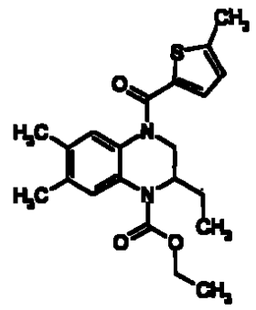
Example 311



2-Ethyl-4-(3-methoxy-4-methyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 411 (MH+).

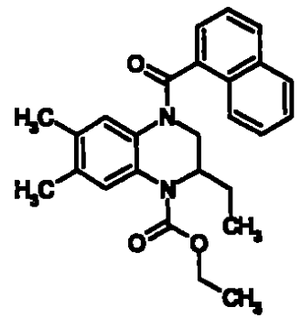
Example 312



2-Ethyl-6,7-dimethyl-4-(5-methyl-thiophene-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 387 (MH+).

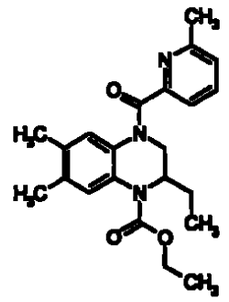
Example 313



2-Ethyl-6,7-dimethyl-4-(naphthalene-1-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):417 (MH+).

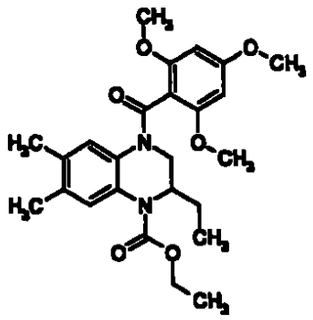
Example 314



2-Ethyl-6,7-dimethyl-4-(6-methyl-pyridine-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):382 (MH+).

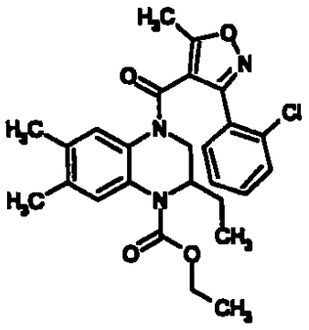
Example 315



2-Ethyl-6,7-dimethyl-4-(2,4,6-trimethoxy-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 457 (MH+).

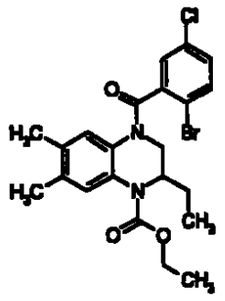
Example 316



4-[3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carbonyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 482 (MH+).

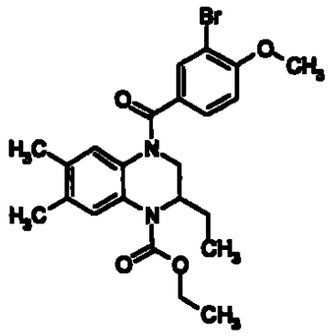
Example 317



4-(2-Bromo-5-chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 480 (MH+).

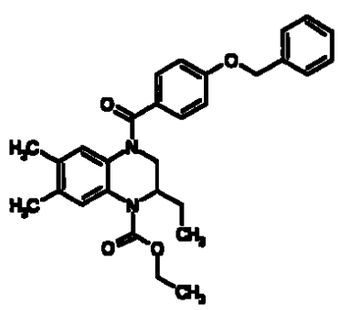
Example 318



4-(3-Bromo-4-methoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):476 (MH+).

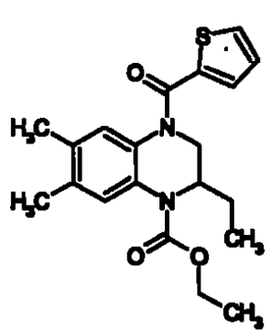
Example 319



4-(4-Benzyloxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):473 (MH+).

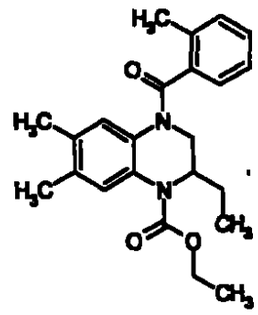
Example 320



2-Ethyl-6,7-dimethyl-4-(thiophene-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):373 (MH+).

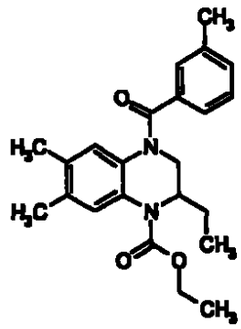
Example 321



2-Ethyl-6,7-dimethyl-4-(2-methyl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 381 (MH+).

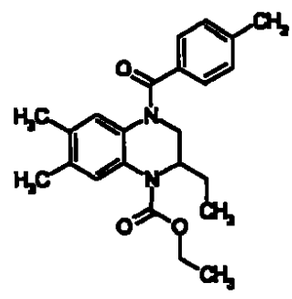
Example 322



2-Ethyl-6,7-dimethyl-4-(3-methyl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 381 (MH+).

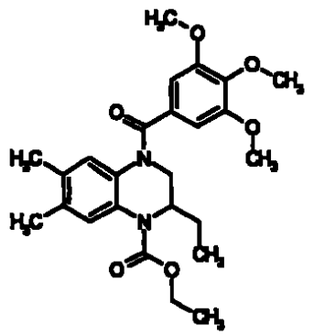
Example 323



2-Ethyl-6,7-dimethyl-4-(4-methyl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

'LC-MS (ESI+): (MH+).

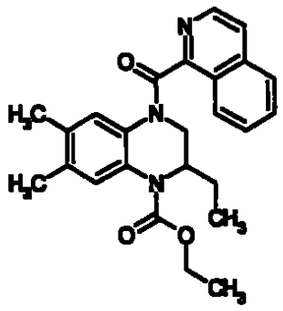
Example 324



2-Ethyl-6,7-dimethyl-4-(3,4,5-trimethoxy-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 457 (MH+).

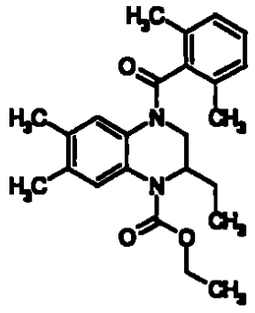
Example 325



2-Ethyl-4-(isoquinoline-1-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 418 (MH+).

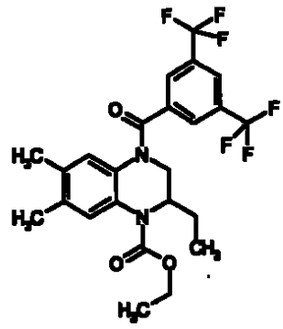
Example 326



4-(2,6-Dimethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 395 (MH+).

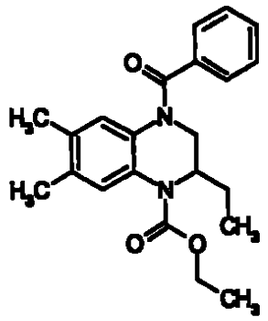
Example 327



4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 503 (MH+).

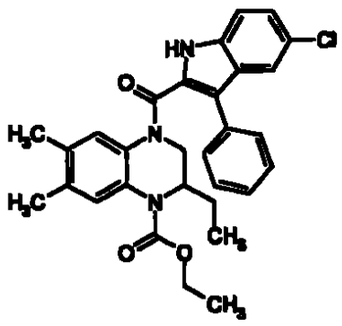
Example 328



4-Benzoyl-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 367 (MH+).

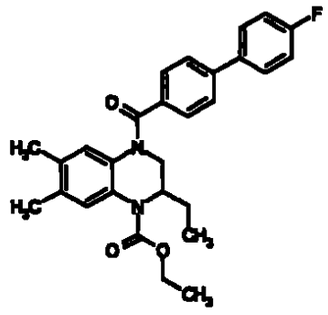
Example 329



4-(5-Chloro-3-phenyl-1H-indole-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 517 (MH+).

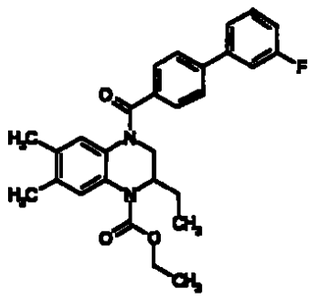
Example 330



2-Ethyl-4-(4'-fluoro-biphenyl-4-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):461 (MH+).

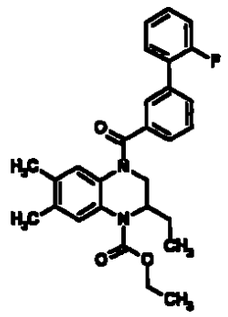
Example 331



2-Ethyl-4-(3'-fluoro-biphenyl-4-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 461 (MH+).

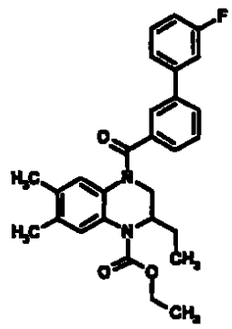
Example 332



2-Ethyl-4-(2'-fluoro-biphenyl-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):461 (MH+).

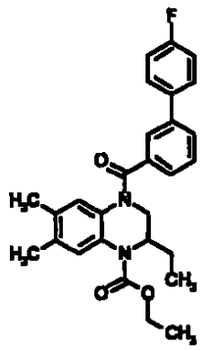
Example 333



2-Ethyl-4-(3'-fluoro-biphenyl-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):461 (MH+).

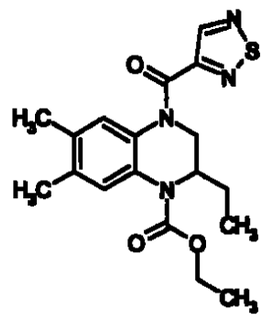
Example 334



2-Ethyl-4-(4'-fluoro-biphenyl-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 461 (MH+).

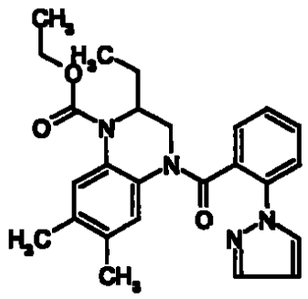
Example 335



2-Ethyl-6,7-dimethyl-4-([1,2,5]thiadiazole-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):375 (MH+).

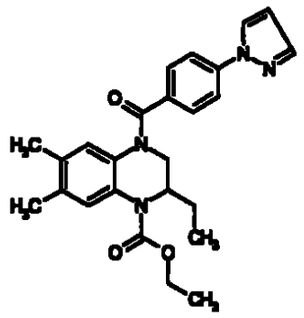
Example 336



2-Ethyl-6,7-dimethyl-4-(2-pyrazol-1-yl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 433 (MH+).

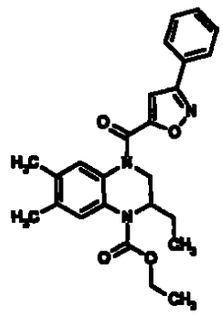
Example 337



2-Ethyl-6,7-dimethyl-4-(4-pyrazol-1-yl-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 433 (MH+).

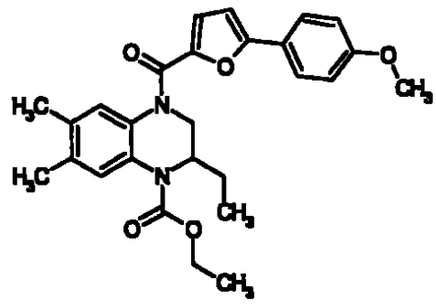
Example 338



2-Ethyl-6,7-dimethyl-4-(3-phenyl-isoxazole-5-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 434 (MH+).

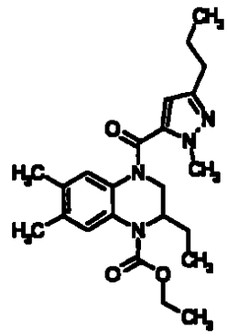
Example 339



2-Ethyl-4-[5-(4-methoxy-phenyl)-furan-2-carbonyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 463 (MH+).

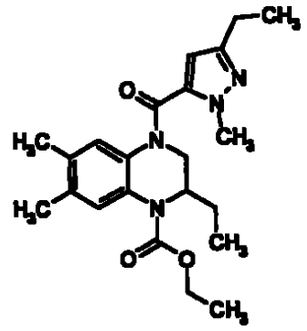
Example 340



2-Ethyl-6,7-dimethyl-4-(2-methyl-5-propyl-2H-pyrazole-3-carbonyl)- 3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 413(MH+).

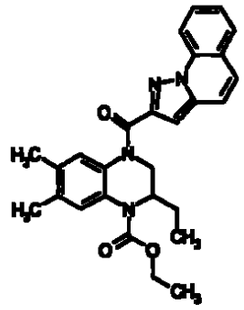
Example 341



2-Ethyl-4-(5-ethyl-2-methyl-2H-pyrazole-3-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):399 (MH+).

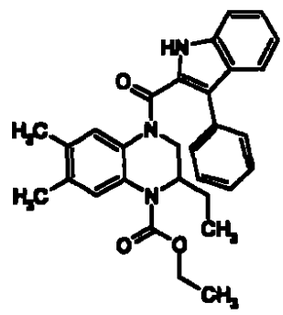
Example 342



2-Ethyl-6,7-dimethyl-4-(pyrazolo[1,5-a]quinoline-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 457 (MH+).

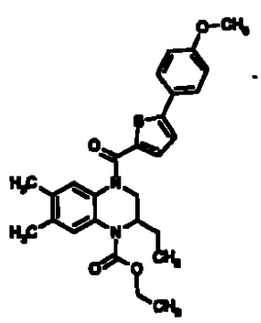
Example 343



2-Ethyl-6,7-dimethyl-4-(3-phenyl-1H-indole-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):482 (MH+).

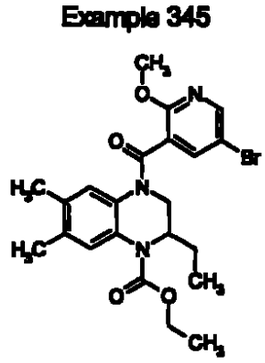
Example 344



2-Ethyl-4-[5-(4-methoxy-phenyl)-thiophene-2-carbonyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):479 (MH+).

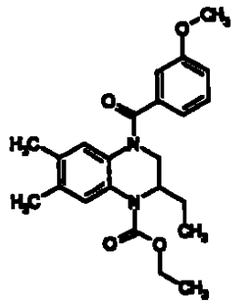
Example 345



4-(5-Bromo-2-methoxy-pyridine-3-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 477 (MH+).

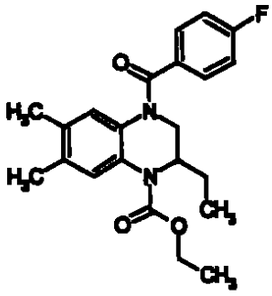
Example 346



2-Ethyl-4-(3-methoxy-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 397 (MH+).

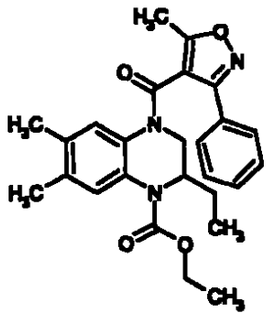
Example 347



2-Ethyl-4-(4-fluoro-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 385 (MH+).

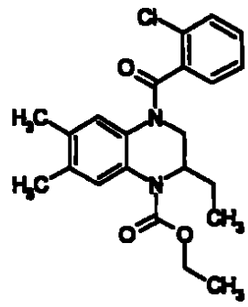
Example 348



2-Ethyl-6,7-dimethyl-4-(5-methyl-3-phenyl-isoxazole-4-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 448 (MH+).

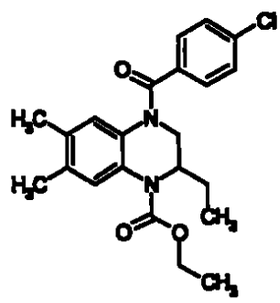
Example 349



4-(2-Chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 401 (MH+).

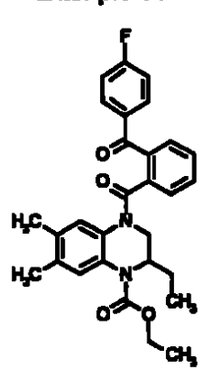
Example 350



4-(4-Chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):401 (MH+).

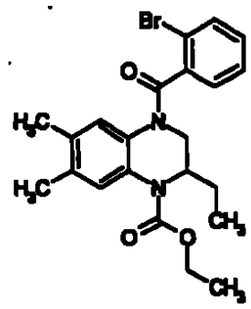
Example 351



2-Ethyl-4-[2-(4-fluoro-benzoyl)-benzoyl]-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 489 (MH+).

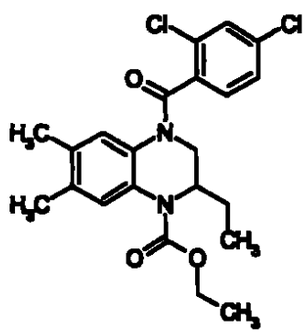
Example 352



4-(2-Bromo-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 446 (MH+).

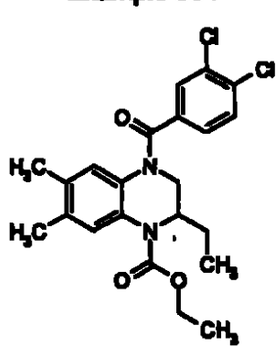
Example 353



4-(2,4-Dichloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 436 (MH+).

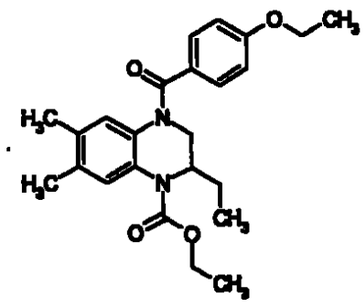
Example 354



4-(3,4-Dichloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 436 (MH+).

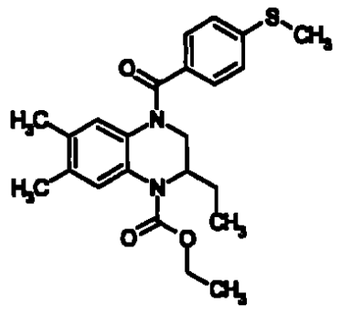
Example 355



4-(4-Ethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 411 (MH+).

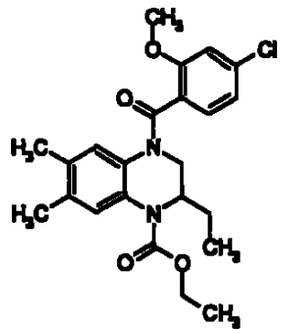
Example 356



2-Ethyl-6,7-dimethyl-4-(4-methylsulfanyl-benzoyl)-3,4-dihydro-2H- quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 413 (MH+).

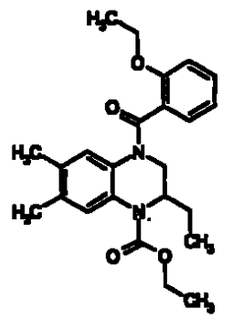
Example 357



4-(4-Chloro-2-methoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 431 (MH+).

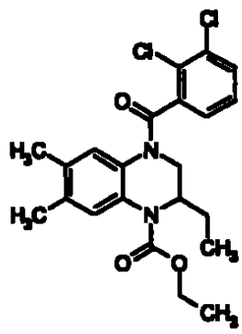
Example 358



4-(2-Ethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 411 (MH+).

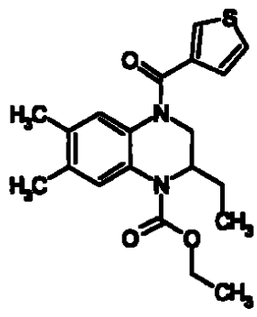
Example 359



4-(2,3-Dichloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 436 (MH+).

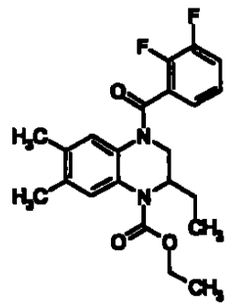
Example 360



2-Ethyl-6,7-dimethyl-4-(thiophene-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 373 (MH+).

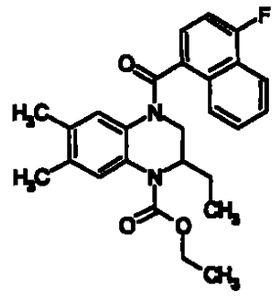
Example 361



4-(2,3-Difluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 403 (MH+).

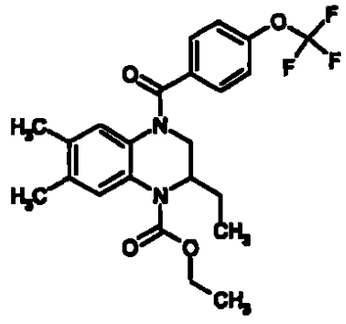
Example 362



2-Ethyl-4-(4-fluoro-naphthalene-1-carbonyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 435 (MH+).

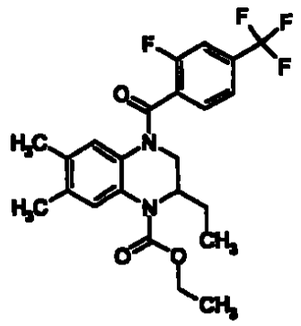
Example 363



2-Ethyl-6,7-dimethyl-4-(4-trifluoromethoxy-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 451 (MH+).

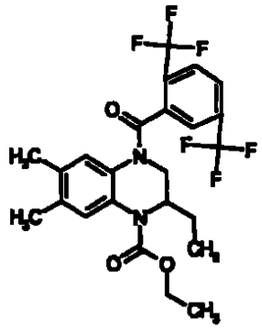
Example 364



2-Ethyl-4-(2-fluoro-4-trifluoromethyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 453 (MH+).

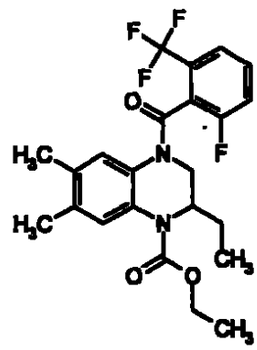
Example 365



4-(2,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 503 (MH+).

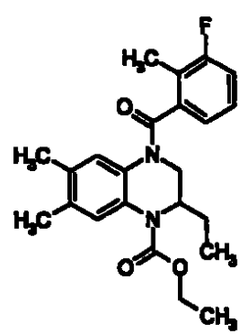
Example 366



2-Ethyl-4-(2-fluoro-6-trifluoromethyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 453 (MH+).

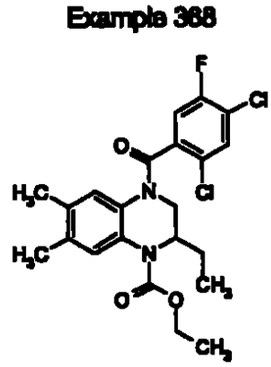
Example 367



2-Ethyl-4-(3-fluoro-2-methyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 399 (MH+).

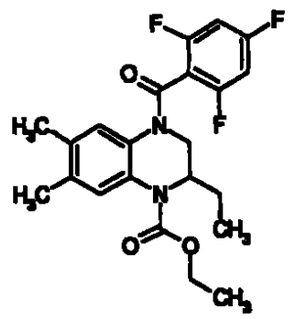
Example 368



4-(2,4-Dichloro-5-fluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 454 (MH+).

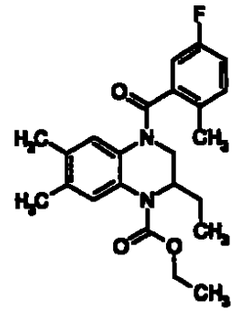
Example 369



2-Ethyl-6,7-dimethyl-4-(2,4,6-trifluoro-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 421 (MH+).

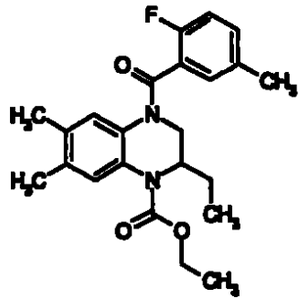
Example 370



2-Ethyl-4-(5-fluoro-2-methyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 399 (MH+).

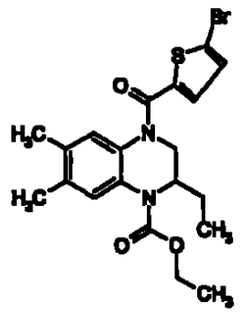
Example 371



2-Ethyl-4-(2-fluoro-5-methyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-=quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 399 (MH+).

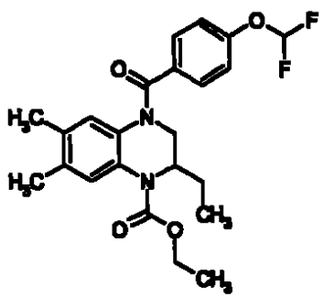
Example 372



4-(5-Bromo-thiophene-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 452 (MH+).

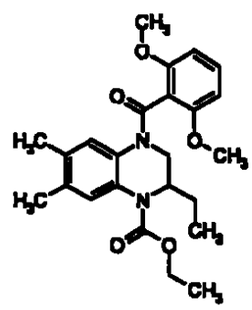
Example 373



4-(4-Difluoromethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):433 (MH+).

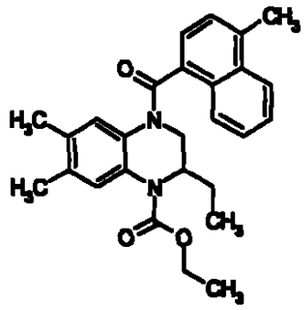
Example 374



4-(2,6-Dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 427 (MH+).

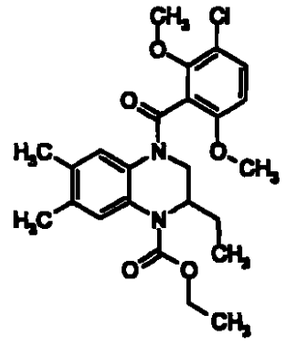
Example 375



2-Ethyl-6,7-dimethyl-4-(4-methyl-naphthalene-1-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 431 (MH+).

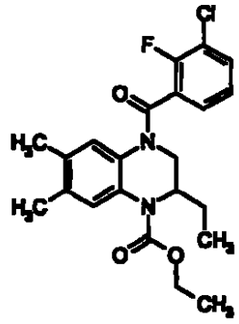
Example 376



4-(3-Chloro-2,6-dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):461 (MH+).

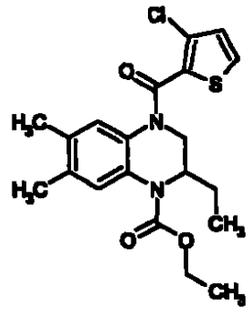
Example 377



4-(3-Chloro-2-fluoro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 419 (MH+).

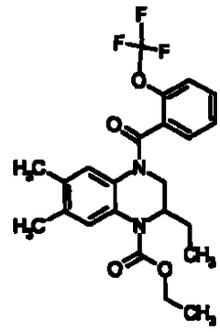
Example 378



4-(3-Chloro-thiophene-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 407 (MH+).

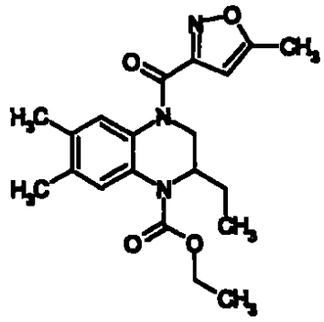
Example 379



2-Ethyl-6,7-dimethyl-4-(2-trifluoromethoxy-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):451 (MH+).

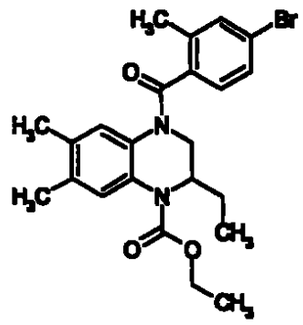
Example 380



2-Ethyl-6,7-dimethyl-4-(5-methyl-isoxazole-3-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 372 (MH+).

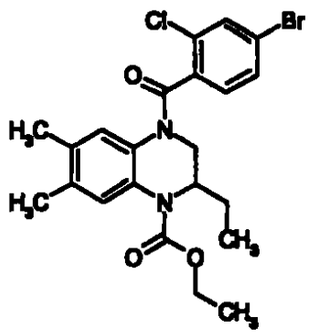
Example 381



2-Ethyl-6,7-dimethyl-4-(3-methyl-furan-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 371 (MH+).

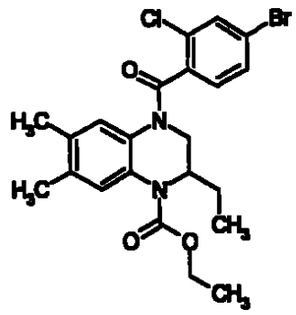
Example 382



4-(4-Bromo-2-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

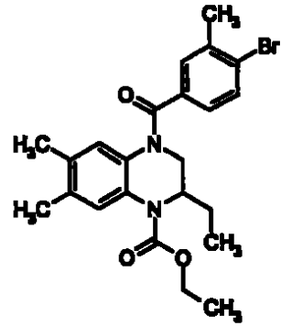
Example 383



4-(4-Bromo-2-chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

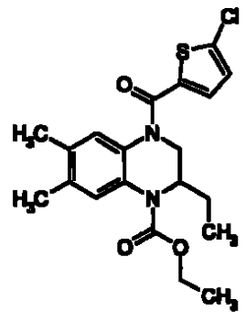
Example 384



4-(4-Bromo-3-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

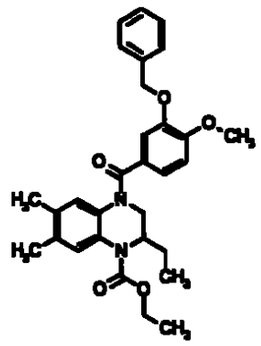
Example 385



4-(5-Chloro-thiophene-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 407 (MH+).

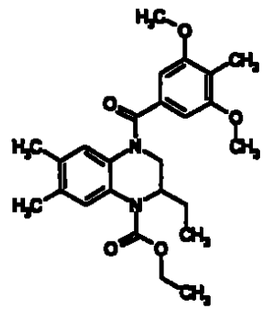
Example 386



4-(3-Benzyloxy-4-methoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 503 (MH+).

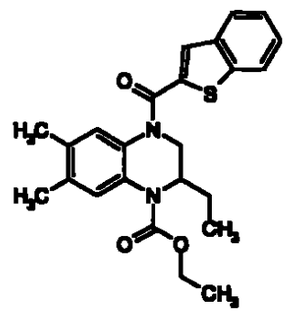
Example 387



4-(3,5-Dimethoxy-4-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 441 (MH+).

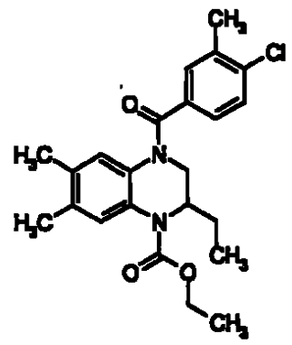
Example 388



4-(Benzo[b]thiophene-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 423 (MH+).

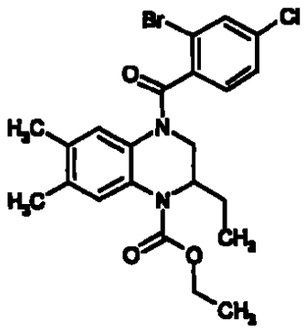
Example 389



4-(4-Chloro-3-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 415 (MH+).

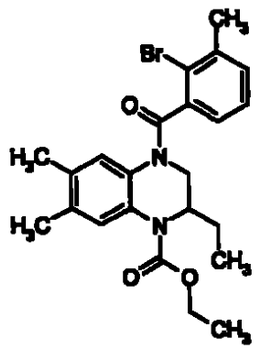
Example 390



4-(2-Bromo-4-chloro-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 480 (MH+).

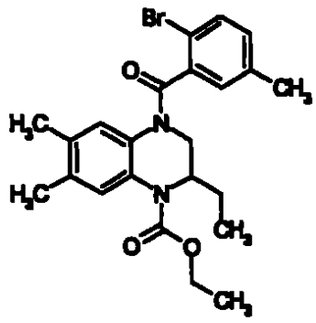
Example 391



4-(2-Bromo-3-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

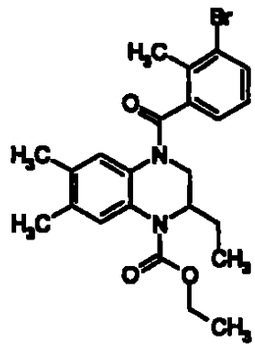
Example 392



4-(2-Bromo-5-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

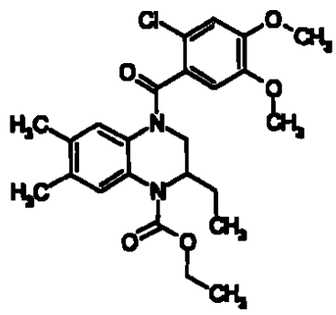
Example 393



4-(3-Bromo-2-methyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 460 (MH+).

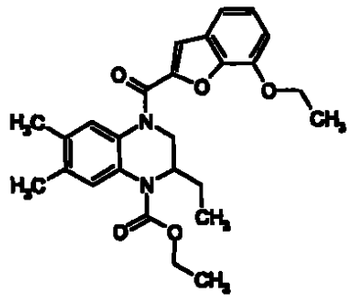
Example 394



4-(2-Chloro-4,5-dimethoxy-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):461 (MH+).

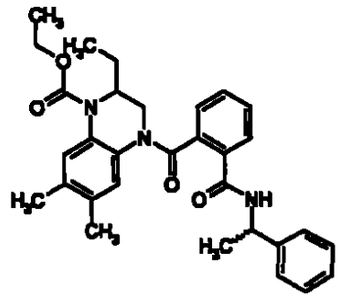
Example 395



4-(7-Ethoxy-benzofuran-2-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 451 (MH+).

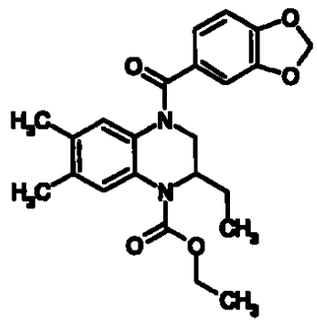
Example 396



2-Ethyl-6,7-dimethyl-4-[2-(1-phenyl-ethylcarbamoyl)-benzoyl]-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 514 (MH+).

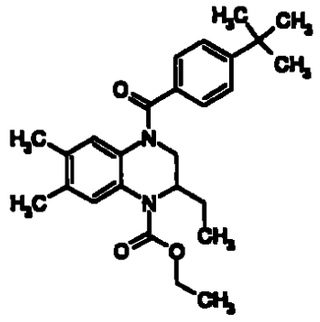
Example 397



4-(Benzo[1,3]dioxole-5-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 411 (MH+).

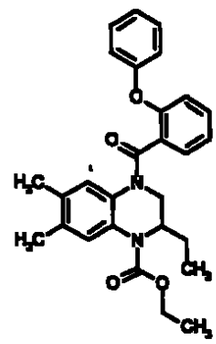
Example 398



4-(4-tert-Butyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):423 (MH+).

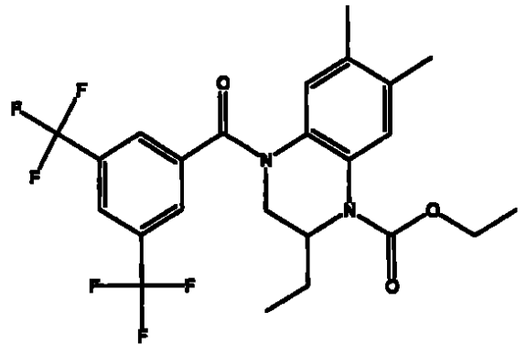
Example 399



2-Ethyl-6,7-dimethyl-4-(2-phenoxy-benzoyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 459 (MH+).

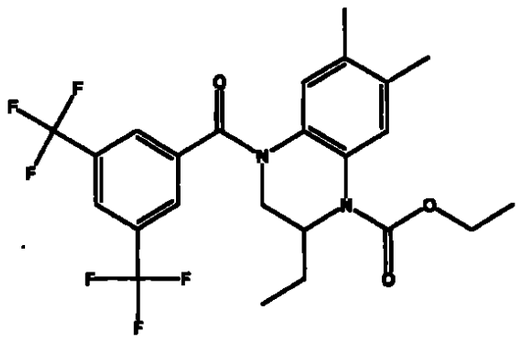
Example 400



4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 503 (MH+).

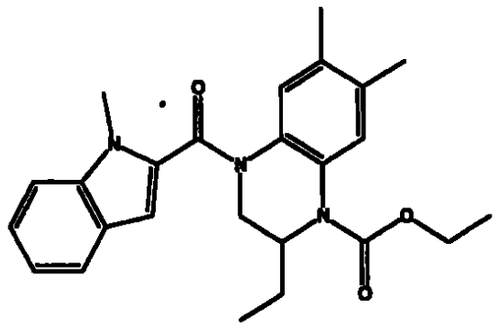
Example 401



4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 503 (MH+).

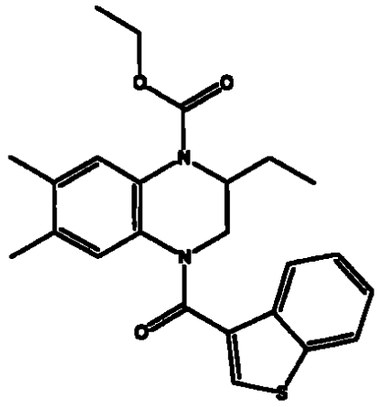
Example 402



2-Ethyl-6,7-dimethyl-4-(1-methyl-1H-indole-2-carbonyl)-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 420 (MH+).

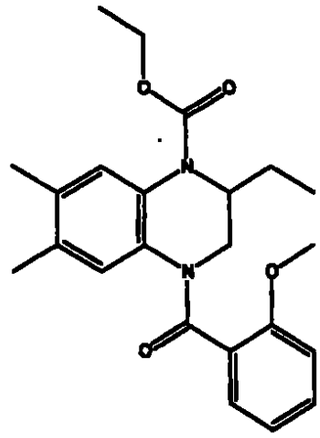
Example 403



4-(Benzo[b]thiophene-3-carbonyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 423 (MH+).

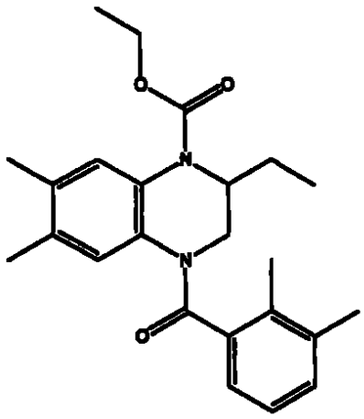
Example 404



2-Ethyl-4-(2-methoxy-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):397 (MH+).

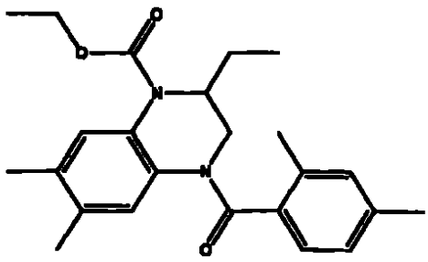
Example 405



4-(2,3-Dimethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):395 (MH+).

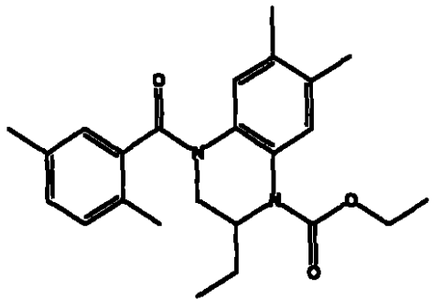
Example 406



4-(2,4-Dimethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):395 (MH+).

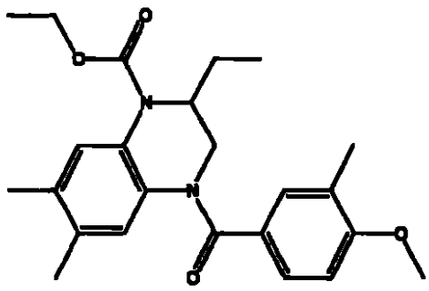
Example 407



4-(2,5-Dimethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+): 395 (MH+).

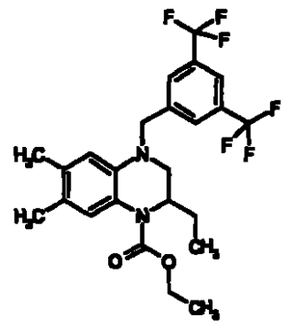
Example 408



2-Ethyl-4-(4-methoxy-3-methyl-benzoyl)-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

LC-MS (ESI+):411 (MH+).

Example 409



Preparation of 4-(3,5-Bis-trifluoromethyl-benzyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

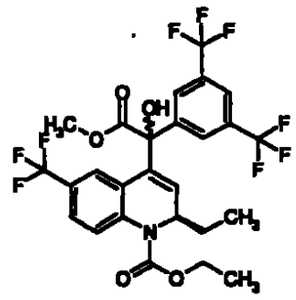
A solution of 2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester (0.05g, 1eq, 0.19mmol), 3,5-bis-(trifluoromethyl)benzyl bromide (0.038mL, 2.2eq, 0.42mmol) and triethylamine (0.062mL, 3eq, 0.57mmol) in acetonitrile (2mL) was treated with catalytic potassium iodide and subjected to two ten minute cycles on the Emrys Optimizer (Personal Chemistry, Uppsala, Sweden) chemical microwave at 180°C. The reaction was evaporated to dryness and purified on the Shimadzu Corporation (Kyoto, Japan) preparative HPLC system using a 40-100% acetonitrile/water 6 min gradient, 8min total run time to provide the title compound (0.0045mg, 5%).

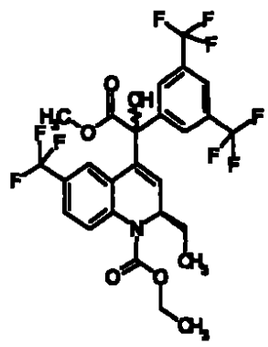
^{1}HNMR (CDCl3): δ 0.90 (t, J=7.47Hz, 3H), 1.31 (t, J=7.05Hz, 3H), 1.46 (m, 2H), 2.11 (s, 3H), 2.16 (s, 3H), 3.17 (dd, J=11.28, 1.24Hz, 1H), 3.49 (dd, J=11.16, 4.15Hz, 1H), 4.19 (m, 1H), 4.28 (m, 1H), 4.46 (d, J=17.43Hz), 4.52 (m, 1H), 4.66 (d, J=17.01Hz, 1H), 6.31 (s, 1H), 7.29 (brs, 1H), 7.71 (s, 2H), 7.78 (s, 1H).

LCMS (ESI+): 489 (MH+).

The prophetic examples 410-427 may be prepared in optically enriched form by resolution of the corresponding racemate indicated, or an intermediate in its synthesis, using methods analogous to those described herein:

Example 410 (Stereo-Isomers of Example 2)





(*R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

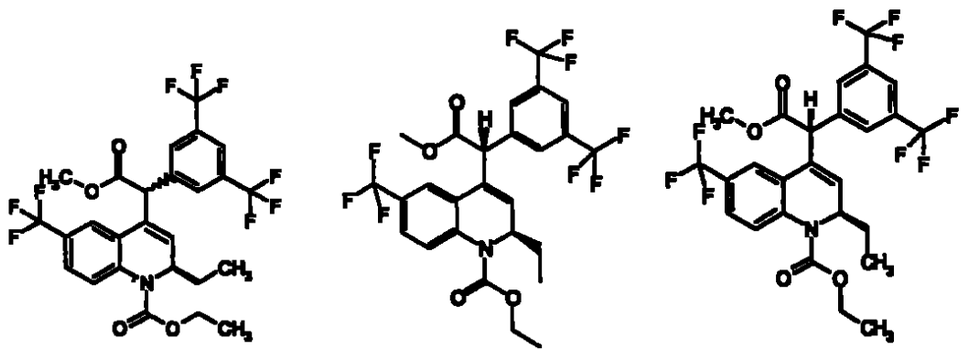
(*R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*S*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester; or

(*S*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

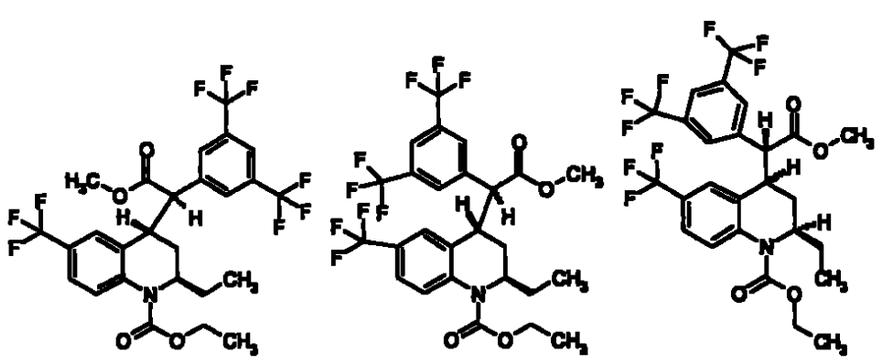
Example 411 (Stereo-isomers of Examples 3 and 4)



(S, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester; or

(S, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester; or a pharmaceutically acceptable salt of said compound.

Example 412 (Stereo-isomers of Examples 5, 6, 7 and 8)



(*R*, *S*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*S, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

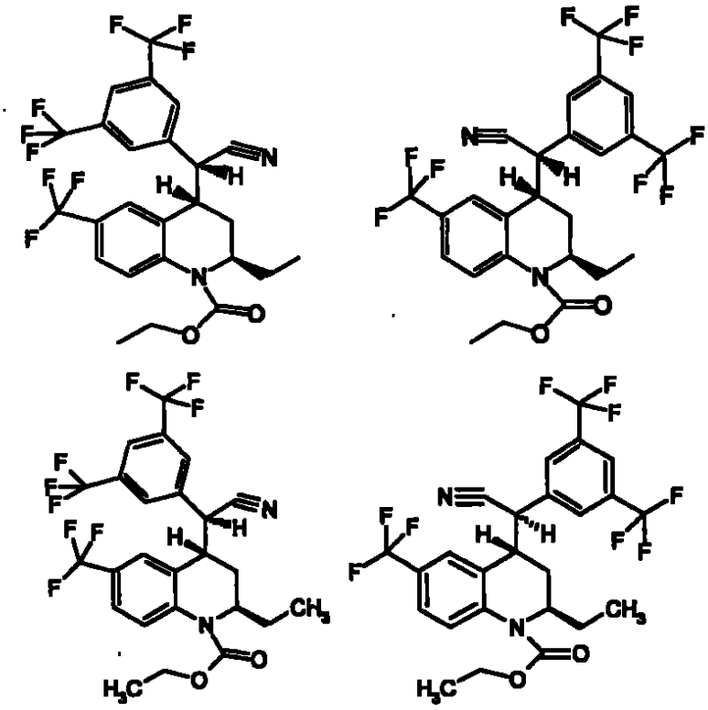
(*S, S, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*S, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester; or

(*S, R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester; or

a pharmaceutically acceptable salt of said compound.

Example 413 (Stereo-Isomers of Examples 9 and 10)



(*R, R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*S*, *S*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*S*, *S*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*S*, *R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*S*, *R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

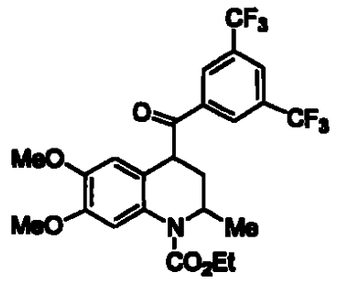
(*R*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*S*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester; or

(*S*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 414 (Stereo-Isomers of Examples 13 and 14)



(*R*,*S*)-4-[(3,5-bis-trifluoromethyl-benzoyl)]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

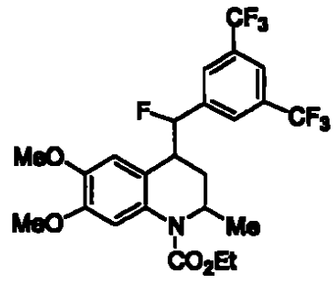
(*R*,*R*)-4-[(3,5-Bis-trifluoromethyl-benzoyl)]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,R*)-4-[(3,5-bis-trifluoromethyl-benzoyl)]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; or

(*S,S*)-4-[(3,5-Bis-trifluoromethyl-benzoyl)]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt thereof.

Example 415 (Stereo-isomers of Examples 18, 19 and 35)



(*R,R,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,R,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

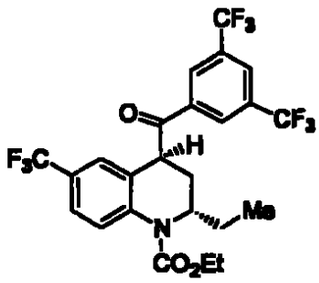
(*S,R,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

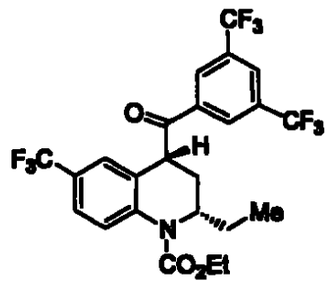
(*S,S,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; or

(*S,S,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 416 (Stereo-isomers of Examples 20 and 21)



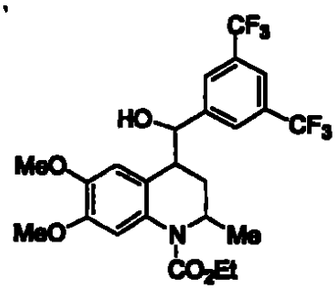


(*S,R*)-4-[(3,5-bis-trifluoromethyl-benzoyl)]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; or

(*S,S*)-4-[(3,5-bis-trifluoromethyl-benzoyl)]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 417 (Stereo-isomers of Examples 16 and 17)



(*R,R,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,R,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

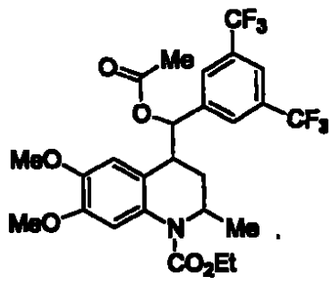
(*S,R,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,S,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; or

(*S,S,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 418 (Stereo-isomers of Example 34)



(*R,S,S*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,S,S*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

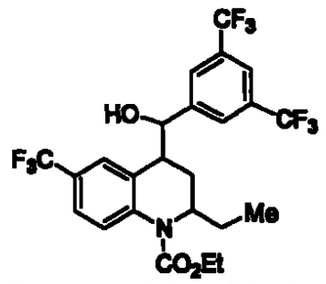
(*S,R,S*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,S,R*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; or

(*S,R,R*)-4-[Acetoxy-(3,5-Bis-trifluoromethyl-phenyl)-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 419 (Stereo-isomers of Examples 22, 23, 24 and 25)



(*R,S,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,S,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

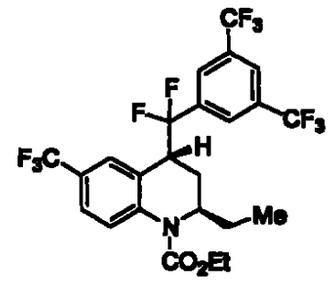
(*S,S,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,R,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; or

(*S,R,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 420



4-[(3,5-Bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

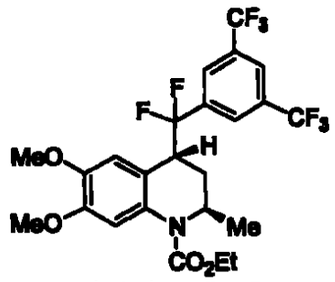
(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester; or

(*S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 421 (Stereo-isomers of Example 15)



(*R,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-methyl-6,7-dimethoxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

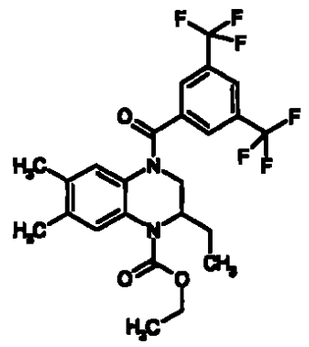
(*R,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-methyl-6,7-dimethoxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*S,R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-methyl-6,7-dimethoxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester; or

(*S,S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl]-2-methyl-6,7-dimethoxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 422 (Stereo-isomers of Example 182)

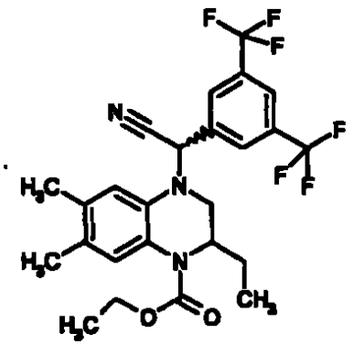


(*R*)-4-[(3,5-Bis-trifluoromethyl-benzoyl)]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester; or

(*S*)-4-[(3,5-Bis-trifluoromethyl-benzoyl)]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 423 (Stereo-isomers of Example 178)



(*R*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

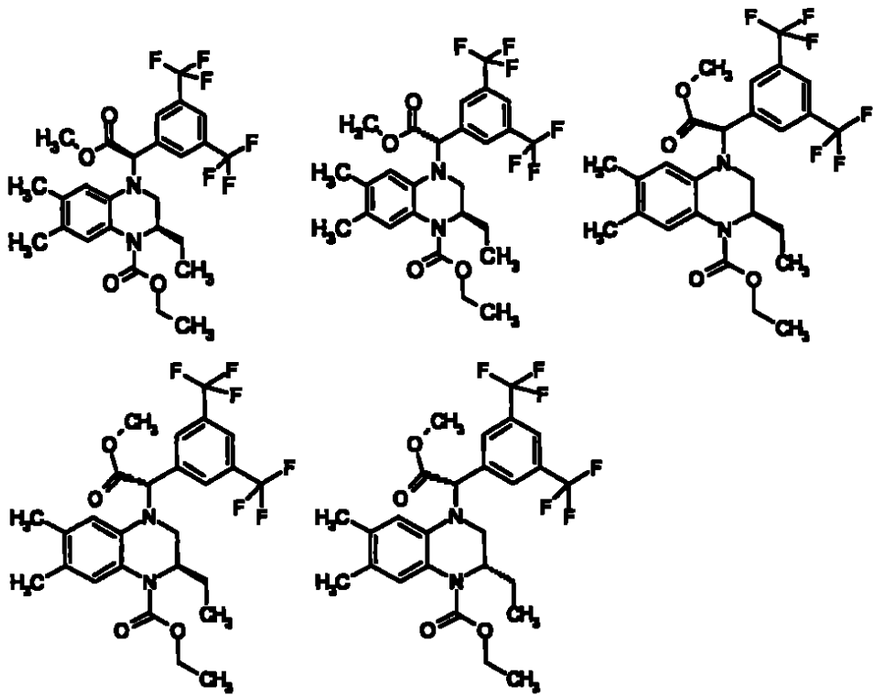
(*R*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*S*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester; or

(*S*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 424 (Stereo-isomers of Examples 170, 171, 172, and 173)



(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

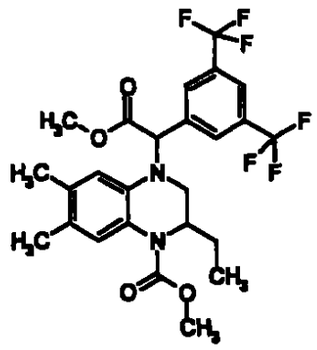
(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester; or

(*S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 425 (Stereo-isomers of Examples 174 and 175)



(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester;

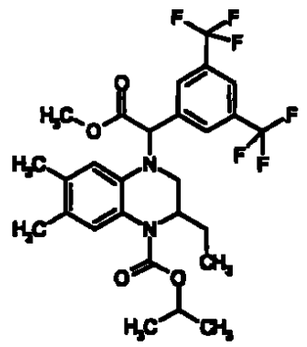
(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester;

(*S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester; or

(*S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 426 (Stereo-isomers of Examples 176 and 177)



(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester;

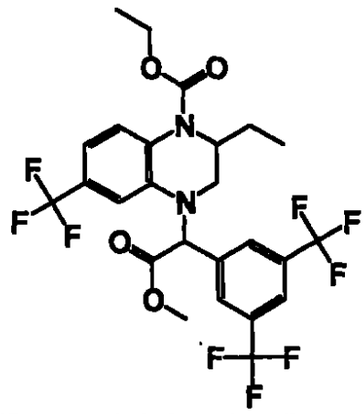
(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester;

(*S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester; or

(*S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester;

or a pharmaceutically acceptable salt of said compound.

Example 427 (Stereo-Isomers of Example 183)



(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

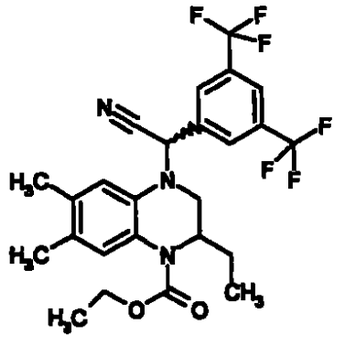
(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester; or

(*S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

Examples 428 and 429



(*R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester and

(*R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester

A mixture of 2-ethyl-6,7-dimethyl-3,4-dihydro-2(R)-H-quinoxaline-1-carboxylic acid ethyl ester (1g, 1eq, 3.81mmol), 3,5-bis-(trifluoromethyl-phenyl)-bromo-acetonitrile (Preparation 40, 1.27gm, 1eq, 3.81mmol) and 2,6-lutidine (3eq, 11.43mmol) in N,N-dimethylformamide (5mL) was stirred at room temperature for 24 hours. The reaction was partitioned between ethyl acetate and water, and the phases were separated. The aqueous phase was extracted 3 times with ethyl acetate, and the combined organic extracts were washed 2 times with water, 1 time with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Chromatography on silica gel using a gradient of 10-30% ethyl acetate in hexanes as eluant provided the desired nitrile diastereoisomers (1.5:1) (1.0g. and 0.7g, 60%).

Isomer 1:

LCMS (ESI+): 514 (MH+)

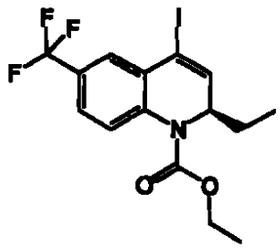
^{1}H-NMR ($CDCl_3$) δ 0.88 (t, J=7.5Hz, 3H), 1.29 (t, J=7.1Hz, 3H), 1.49 (m, 2H), 2.21 (s, 3H), 2.22 (s, 3H), 3.03 (dd, J_1=11.0Hz, J_2=2.9Hz, 1H), 3.19 (dd, J_1=11.0Hz, J_2=5.4Hz, 1H), 4.19 (m, 1H), 4.27 (m, 1H), 4.50 (brm, 1H), 6.05 (s, 1H), 6.59 (s, 1H), 7.33 (brs, 1H), 7.94 (s, 1H), 7.97 (s, 2H).

Isomer2:

LCMS (ESI+): 514 (MH+)

^{1}H-NMR ($CDCl_3$) δ 0.76 (t, J=7.48 Hz, 3H), 1.31 (t, J=7.06Hz, 3H), 1.52 (m, 2H), 2.21 (s, 3H), 2.23 (s, 3H), 2.75 (dd, J_1=11.0Hz, J_2=2.1Hz, 1H), 3.29 (dd, J_1=11.0Hz, J_2=3.73Hz, 1H), 4.19-4.30 (m, 2H), 4.52 (brm, 1H), 6.19 (s, 1H), 6.70 (s,1H), 7.47 (brs, 1H), 7.96 (s, 1H), 8.00 (s, 2H).

Preparation 42



(*R*)-2-Ethyl-4-Iodo-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

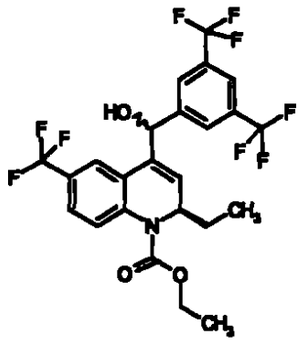
The title compound was prepared using the general procedure described by D.H.R. Barton et al. (Tetrahedron Letters 1983 *24*, 1605). To a solution of Iodine

(3.0gm, 9.1mmol) in anhydrous tetrahydrofuran (30mL) under nitrogen was slowly added a solution of 1,1,3,3-tetramethylguanidine (63.7mmol, 8mL) in anhydrous tetrahydrofuran (30mL). The mixture was stirred at room temperature for 10min before addition of (*R*)-2-ethyl-4-hydrazono-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 6, 9.1mmol, 3gm) in anhydrous tetrahydrofuran (30mL). After 15min the solvent was removed under vacuum and the residue heated under nitrogen at 85°C for 90min. The residue was dissolved in ethyl acetate, washed with 2N hydrochloric acid, aqueous sodium sulfite solution (2.5%), saturated sodium hydrogen carbonate solution and dried over anhydrous sodium sulfate. The crude product was purified by chromatography on silica gel eluting with hexanes/ethyl acetate from 19:1 to 85:15 to give the title compound as a yellow solid (2.8gm, 72%).

MS: 426.3 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.69 (brs, 1H), 7.61 (brd, J = 8.14Hz, 1H), 7.49 (brd, J = 8.14Hz, 1H), 6.85 (d, J = 6.64Hz, 1H), 4.87 (m, 1H), 4.27 (m, 2H), 4.15 (m, 1H), 1.50 (m, 1H), 1.38 (m, 1H), 1.32 (t, J=7.47Hz, 3H), 0.87 (t, J=7.47Hz, 3H).

Example 430



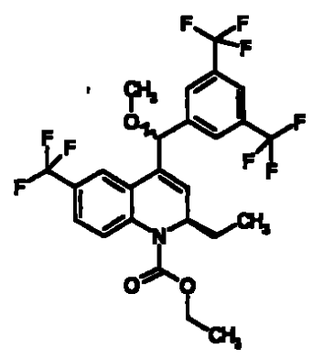
(*RS, RS*) and (*RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*RS*)-2-ethyl-4-iodo-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (814mg, 1.91mmol, prepared as described above for the (*R*) isomer except that racemic starting material was used) in anhydrous tetrahydrofuran (4mL) under nitrogen at -78°C was added dropwise n-butyllithium (2.5M in hexanes, 2.87mmol, 1.15mL). After 5min 3,5-bis(trifluoromethyl)benzaldehyde (6.06mmol, 1mL) was added dropwise. After 45min at -78°C the mixture was allowed to warm to room temperature and after 1hr water

was added. The mixture was acidified by addition of 2N hydrochloric acid and extracted with ethyl acetate. The organic solution was washed with water, dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by chromatography on silica gel eluting with hexanes/ethyl acetate from 9:1 to 4:1 then further purified by chromatography on silica gel eluting with dichloromethane to give the title compounds as a mixture of diastereoisomers (60mg).

MS: 540.3 $[M-H]^+$ found.

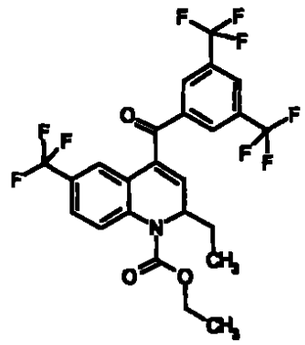
Example 431



(*RS, RS*) and (*RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxy-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of the diastereoisomeric mixture (*RS, RS*) and (*RS, SR*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Example 430, 32mg, 0.059mmol) in dimethylsulfoxide (3mL) under nitrogen was added powdered potassium hydroxide (0.236mmol, 13mg) followed immediately by iodomethane (0.118mmol, 7.4µL). The mixture was stirred at room temperature for 2hr then diluted with 2N hydrochloric acid. The mixture was extracted with ethyl acetate, the organic layer washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was purified by chromatography on silica gel eluting with hexanes then hexanes/ethyl acetate 19:1 then 9:1 then 85:15 to give the title compound (13mg) as a mixture of diastereoisomers.

Example 432



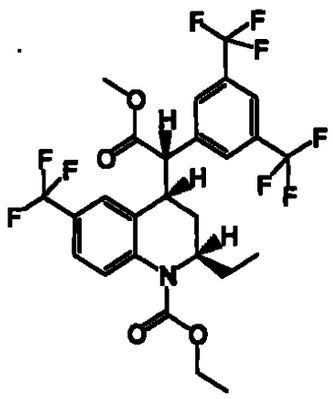
(*RS*)-4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of the diastereoisomeric mixture (*RS, RS*) and (*RS, SR*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Example 430, 11mg, 0.020mmol) in anhydrous diethyl ether (1mL) was added manganese (IV) oxide (22mg, activated, ~85%, Aldrich Chemical Company, Milwaukee, WI). The suspension was stirred at ambient temperature for 90 min. A second aliquot of manganese (IV) oxide (20mg) was added and stirring was continued for a further 1hr before a third aliquot of manganese (IV) oxide (30mg) was added. After 10min the solid was removed by filtration through Celite®, the solvent was removed under vacuum and the residue was chromatographed on Baker Silica Gel (1gm, 40 µm) (J.T. Baker, Phillipsburg, N.J.) eluting with hexanes then hexanes/ethyl acetate 19:1 then 9:1 then 85:15 then 4:1 to give the title compound (6.6mg).

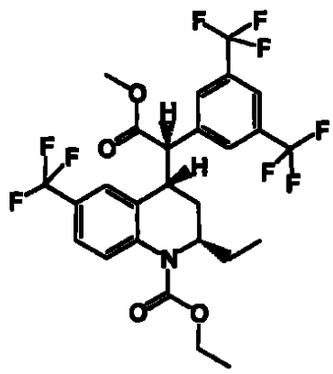
MS: 540.3 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 8.27 (s, 2H), 8.11 (s, 1H), 7.79 (brd, J=8.3Hz, 1H), 7.77 (brs, 1H), 7.57 (brd, J=8.3Hz, 1H), 6.56 (d, J=8.64Hz, 1H), 5.18 (m, 1H), 4.31 (m, 2H), 1.64 (m, 1H), 1.55 (m, 1H), 1.33 (t, J=7.47Hz, 3H), 0.96 (t, J=7.47Hz, 3H).

Examples 433 and 434



(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*S, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

(*RS, RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 7) was resolved on a Pirkle Covalent (S,S)Whelk-O 1 column (Regis Technologies, Inc., Morton Grove, IL) (5 x 25cm) eluting at 100mL/min with 5% ethanol/heptane to provide two fractions:

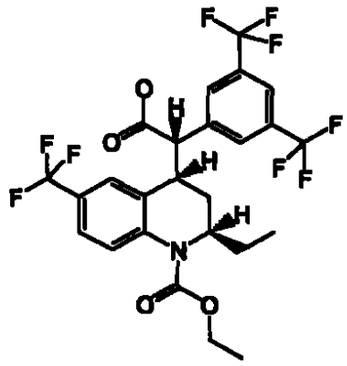
First eluting: (*S, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

MS: 585.8 $[M+H]^+$ found.

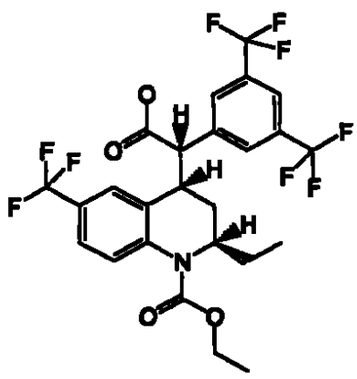
Second eluting: (*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

MS: 586.2 $[M+H]^+$ found.

Examples 435 and 436



(*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A mixture of (*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 433, 98mg, 0.167mmol), aqueous sodium hydroxide (1N, 1mL, 1mmol) and anhydrous tetrahydrofuran (2.4mL) was stirred at room temperature for 5 days before adding 2N hydrochloric acid to acid pH. The mixture was extracted with ethyl acetate, the organic solution washed with water (x3) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue chromatographed on Baker Silica Gel (1gm, 40 µm) (J.T. Baker, Phillipsburg, N.J.) eluting with a hexanes-ethyl acetate gradient from 0% to 80% ethyl acetate to give the title compounds:

First eluting: (*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (67mg);

MS: 572.4 $[M+H]^+$ found.

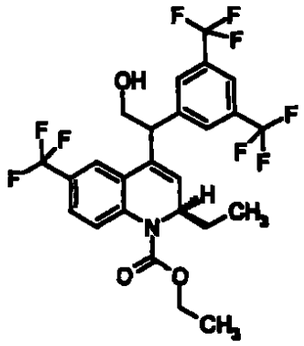
^{1}H-NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.89 (s, 2H), 7.54 (m, 2H), 7.46 (brs, 1H), 4.28 (m, 2H), 4.22 (m, 1H), 4.08 (d, J=11.2Hz, 1H), 3.37 (m, 1H), 1.76 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.31 (t, J=7.05Hz, 3H), 0.95 (m, 1H), 0.70 (t, J=7.47Hz, 3H).

Second eluting: (*R*, *R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (29.5mg)

MS: 572.3 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.94 (s, 2H), 7.83 (s, 1H), 7.50 (d, J=8.14Hz, 1H), 7.41 (brd, J=8.14Hz, 1H), 7.01 (brs, 1H), 4.42 (m, 1H), 4.22 (m, 2H), 4.21 (m, 1H), 3.32 (m,1H), 2.45 (m, 1H), 1.58 (m, 1H), 1.41 (m, 1H), 1.41 (m, 1H), 1.28 (t, J=7.47Hz, 3H), 0.79 (t, J=7.47Hz, 3H).

Example 437



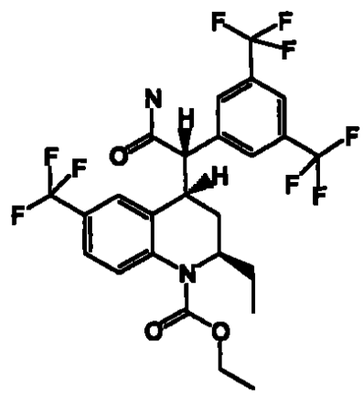
(*R*, *R*) and (*R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester and (*R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Examples 3 and 4, used as the mixture obtained prior to separation, 329mg, 0.563mmol) in anhydrous tetrahydrofuran (6mL) under nitrogen at -40°C was added dropwise a solution of lithium aluminum hydride (1M in tetrahydrofuran, 845μL, 0.845mmol). After 30min an excess of ethyl acetate was added to quench the reaction and the mixture was allowed to warm to room temperature. The mixture was shaken with water/ethyl acetate, the organic layer washed with water, dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was purified by chromatography on silica gel eluting with

hexanes then hexanes/ethyl acetate 9:1 then 4:1 then 7:3 to give the title compounds as a mixture of diastereoisomers (243mg).

MS: 556.3 $[M+H]^+$ found.

Example 438



(*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

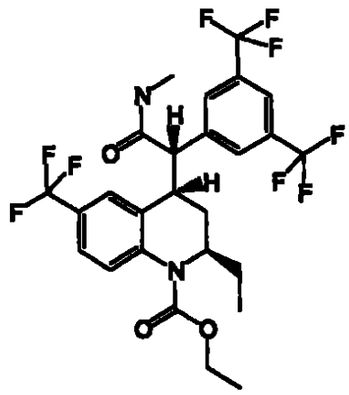
A mixture of (*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 435, 110mg, 0.193mmol) and thionyl chloride (1mL) was stirred at room temperature under nitrogen for 3 days then the excess thionyl chloride was removed under vacuum. To the residue was added a solution of ammonia in dioxane (0.5M, 6mL, 3mmol). After 12hr the mixture was diluted with ethyl acetate, washed with water (x2) and the organic layer was dried over anhydrous sodium sulfate then evaporated to dryness under vacuum. The crude product was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate 39:1 then 19:1 to give the title compound (103mg).

MS: 571.3 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ7.88 (s,1H), 7.88 (s, 2H), 7.51 (m, 2H), 7.46 (brs, 1H), 5.80 (brs, 1H), 5.53 (brs, 1H), 4.26 (m, 1H), 4.26 (m, 1H), 4.19 (m, 1H), 3.82 (d, J=10.79Hz, 1H), 3.45 (m, 1H), 1.68 (m, 1H), 1.49 (m, 1H), 1.39 (m, 1H), 1.29 (t, J=7.06Hz, 3H), 0.95 (m, 1H), 0.70 (t, J=7.47Hz, 3H).

The two following compounds were prepared by an analogous procedure utilizing, respectively, methylamine and dimethylamine in place of ammonia:

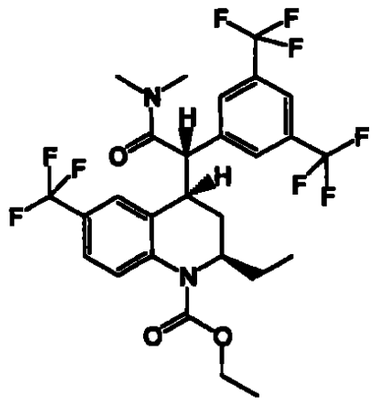
Example 439



(*R*, *P*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methylcarbamoyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

MS: 585.3 $[M+H]^+$ found.

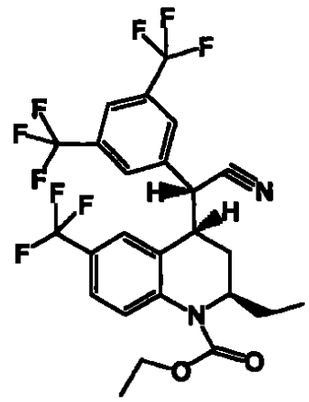
Example 440



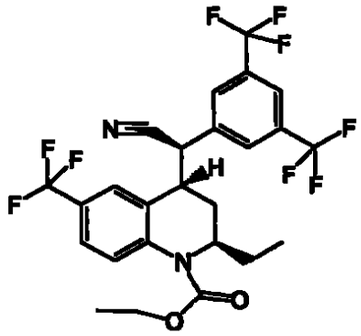
(*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-dimethylcarbamoyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

MS: 599.3 $[M+H]^+$ found.

Examples 441 and 442



(*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 438, 30mg, 0.053mmol) in anhydrous dichloromethane (1mL) was added (methoxycarbonylsulfamoyl)triethylammonium hydroxide (Burgess reagent, 37mg, 0.157mmol). The mixture was stirred at room temperature for 72hr under nitrogen then evaporated under vacuum. The crude product was purified by chromatography on silica gel eluting with hexanes then hexanes/ethyl acetate 19:1 then 9:1 to give the title compounds:

First eluting compound: (*R*, *R*, *R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (8mg);

MS: 553.3 $[M+H]^+$ found;

^{1}H-NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.90 (s, 2H), 7.60 (m, 2H), 7.56 (brs, 1H), 4.68 (d, J=3.32Hz, 1H), 4.28 (m, 1H), 4.22 (m, 1H), 4.22 (m, 1H), 2.93 (m, 1H), 2.22 (m, 1H), 1.63 (m, 1H), 1.62 (m, 1H), 1.51 (m, 1H), 1.27 (t, J=7.47Hz, 3H), 0.83 (t, J=7.47Hz, 3H).

Second eluting compound: (*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (20mg);

MS: 553.3 $[M+H]^+$ found;

^{1}H-NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.92 (s, 2H), 7.59 (brs, 1H), 7.57 (m, 2H), 4.36 (m, 1H), 4.30 (m, 1H), 4.27 (d, J=8.3Hz, 1H), 4.22 (m, 1H), 3.23 (m, 1H), 2.08 (m, 1H), 1.55 (m, 1H), 1.43 (m, 1H), 1.30 (t, J=7.47Hz, 3H), 1.27 (m, 1H), 0.79 (t, J=7.47Hz, 3H).

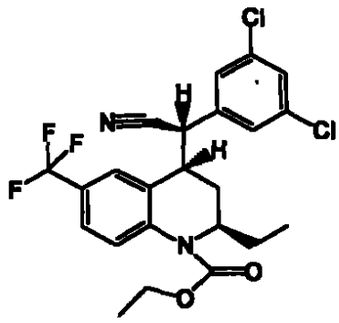
Preparation 43

(*R*)-4-Bromo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

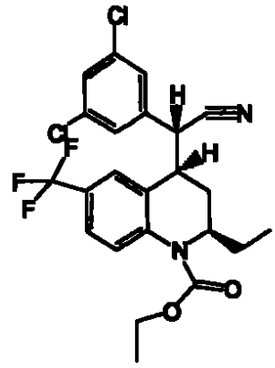
To a solution of (*R*, *S*)-2-ethyl-4-hydroxy-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 13, 3.29gm, 10.37mmol) in dichloromethane (25mL) at ambient temperature under nitrogen was added pyridine (1.58mL) followed dropwise by a solution of phosphorus (III) bromide (1.1mL) in dichloromethane (10mL). The mixture was allowed to stir at ambient temperature for 15h then partitioned between water and dichloromethane. The organic layer was washed with saturated sodium hydrogen carbonate solution (2 x 15mL), dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give the title compound as a yellow oil (3.79gm) containing an approximately 5:1 mixture of diastereoisomers and a variable amount of (*R*)-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester formed by elimination of hydrogen bromide. The crude bromide was used directly without further purification or stored in the refrigerator to arrest further decomposition.

MS: 379, 381 $[M]^{\cdot+}$ found (GC-MS).

Examples 443 and 444



(*R*, *R*, *R*)-4-[Cyano-(3,5-dichloro-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *R*, *S*)-4-[Cyano-(3,5-dichloro-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of 3,5-dichlorophenylacetonitrile (134mg, 0.72mmol, prepared according to the procedure described in WO00/58292) in anhydrous N,N-dimethylformamide (1mL) was added sodium hydride (60% mineral oil dispersion, 0.925mmol, 37mg) and the mixture was stirred at room temperature for 30min. A solution of (*R*)-4-bromo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Preparation 43, 250mg, mixture of isomers as prepared above) in anhydrous N,N-dimethylformamide (1.5mL) was added and the mixture was stirred at room temperature for 5min. Water was added and the mixture was extracted with diethyl ether (3 x 20mL) and the organic extract was diluted with heptane and evaporated to dryness to give the crude product as a yellow oil (~400mg). Initial purification was achieved by purified by chromatography on silica gel eluting with hexanes/ethyl acetate 9:1. Fractions containing the title compounds were further purified using radial chromatography (Chromatron model 7924T, Harrison

Research, Palo Alto, CA) with a 2mm silica gel rotor eluting with hexanes/ethyl acetate 9:1 to give the title compounds:

First eluting compound:

(*R*, *R*, *R*)-4-[cyano-(3,5-dichloro-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (14mg);

^{1}H-NMR ($CDCl_3$) δ 7.59 (s, 2H), 7.54 (s, 1H), 7.43 (t, J=1.95Hz, 1H), 7.35 (d, J=1.95Hz, 2H), 4.69 (d, J=3.52Hz, 1H), 4.28 (m, 1H), 4.22 (m, 1H), 4.22 (m, 1H), 2.90 (m, 1H), 2.27 (m, 1H), 1.61 (m, 1H), 1.50 (m, 1H), 1.49 (m, 1H), 1.29 (t, J=7.03Hz, 3H), 0.84 (t, J=7.42Hz, 3H).

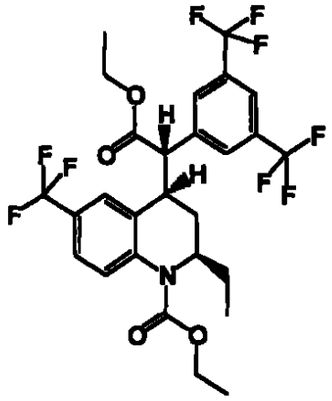
Second eluting compound:

(*R*, *R*, *S*)-4-[cyano-(3,5-dichloro-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (5mg);

MS: 485.2 $[M+H]^+$ found;

^{1}H-NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.55 (s, 2H), 7.42 (t, J=1.66Hz, 1H), 7.33 (d, J=1.66Hz, 2H), 4.34 (m, 1H), 4.27 (m, 1H), 4.22 (m, 1H), 4.01 (d, J=9.13Hz, 1H), 3.13 (m, 1H), 2.07 (m, 1H), 1.53 (m, 1H), 1.42 (m, 1H), 1.30 (t, J=7.47Hz, 3H), 1.16 (m, 1H), 0.78 (t, J=7.47Hz, 3H).

Example 445



(*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-ethoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

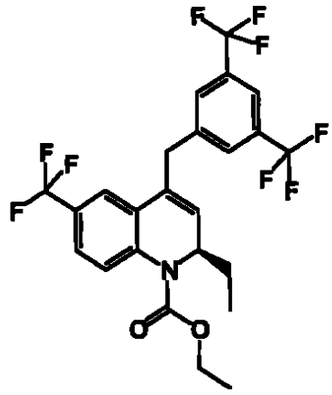
A solution of (*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 435, 33mg, 0.058mmol) in anhydrous ethanol (5mL) containing concentrated sulfuric acid (4 drops) was heated under reflux for 18hr then the solvent was evaporated under vacuum. The residue was partitioned between water and ethyl

acetate, the organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by chromatography on silica gel eluting with hexanes then a hexanes/ethyl acetate gradient from 9:1 to 4:6 to give the title compound (17.5mg) as a gum.

MS: 600.6 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.88 (s, 2H), 7.88 (s, 1H), 7.53 (m, 2H), 7.44 (brs, 1H), 4.35 (m, 1H), 4.27 (m, 2H), 4.22 (m, 1H), 4.06 (m, 1H), 4.01 (d, J=11.62Hz, 1H), 3.37 (m, 1H), 1.73 (m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.30 (t, J=7.06Hz, 3H), 1.27 (t, J=7.06Hz, 3H), 0.94 (m, 1H), 0.70 (t, J=7.47Hz, 3H).

Example 446



(*R*)-4-(3,5-Bis-trifluoromethyl-benzyl)-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

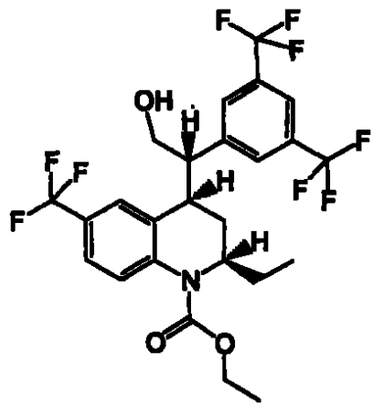
To a solution of (*R, R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester and (*R, S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Examples 3 and 4, used as the mixture obtained prior to separation, 148mg, 0.253mmol) in tetrahydrofuran (3mL) under nitrogen was added aqueous sodium hydroxide solution (1M, 250μL, 0.25mmol). After stirring at room temperature for 72hr an additional aliquot of aqueous sodium hydroxide solution (1M, 100μL, 0.1mmol) was added. After 72hr the mixture was acidified by addition of 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, evaporated under vacuum and the residue was purified by chromatography on silica gel eluting with dichloromethane/hexanes 1:1 then 3:1 followed by dichloromethane then

dichloromethane/methanol 9:1 then a hexanes/ethyl acetate gradient from 9:1 to 4:6 to give the title compound (4.5mg).

MS: 526.3 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.76 (s, 1H), 7.74 (m, 1H), 7.68 (s, 2H), 7.48 (m, 1H), 7.42 (brs, 1H), 5.76 (d, J=5.81Hz, 1H), 4.93 (m, 1H), 4.27 (m, 2H), 3.92 (m, 1H), 3.88(m, 1H), 1.48 (m, 1H), 1.38 (m, 1H), 1.32 (t, J=7.47Hz, 3H), 0.85 (t, J=7.47Hz, 3H).

Example 447



(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 435, 67mg, 0.117mmol) in tetrahydrofuran (1mL) under nitrogen was added borane-dimethylsulfide complex (22.2μL, 0.234mmol). After 24hr aqueous sodium hydroxide (1M, 4 drops) was added to quench the reaction and the mixture was allowed to stir for 1hr. The mixture was acidified by addition of 2N hydrochloric acid, stirred for 10min and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. The crude product was purified by chromatography on silica gel eluting with hexanes then hexanes/ethyl acetate 19:1 then 9:1 then 4:1 then 3:7 and finally 2:3 to give the title compound (54mg).

MS: 558.3 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.80 (s, 2H), 7.60 (brs, 1H), 7.52 (m, 2H), 4.27 (m, 1H), 4.24 (m, 2H), 4.20 (m, 1H), 4.00 (m, 1H), 3.54 (m, 1H), 2.84 (m, 1H), 1.82 (m, 1H), 1.63 (brs, 1H), 1.46 (m, 1H), 1.32 (m, 1H), 1.31 (t, J=7.05Hz, 3H), 0.87 (m, 1H), 0.69 (t, J=7.47Hz, 3H).

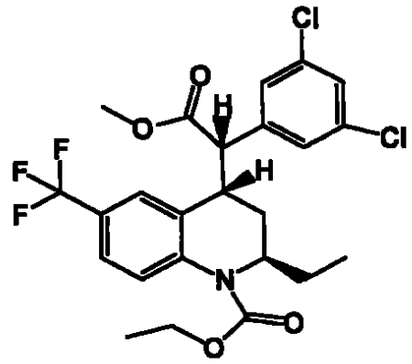
Preparation 44

Methyl (3,5-dichloro)-phenylacetate

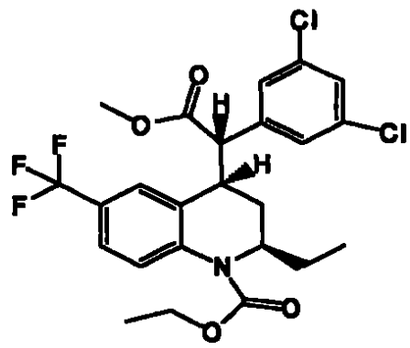
A mixture of 3,5-dichlorophenylacetonitrile (2gm, prepared according to the procedure described in WO00/58292), ethanol (25mL), potassium hydroxide (3.95gm) and water (10mL) was heated under reflux for 4hr then evaporated to dryness under vacuum. The residue was partitioned between water (20mL) and diethyl ether and the aqueous layer was acidified to pH1 by addition of concentrated hydrochloric acid. The mixture was extracted with diethyl ether (3 x 25mL), the organic layer dried over anhydrous sodium sulfate and evaporated under vacuum. The carboxylic acid was dissolved in methanol (20mL) and trimethylsilyldiazomethane (2M solution in hexanes, 30mL, Aldrich Chemical Company, Milwaukee, WI) was added slowly. After 1hr the solvent was removed under vacuum, the residue dissolved in diethyl ether, washed with aqueous sodium carbonate solution (2M), dried over anhydrous sodium sulfate and evaporated to dryness to give the title compound (2.1gm).

^{1}H-NMR ($CDCl_3$) δ 7.27 (s,1H), 7.17 (s, 2H), 3.71 (s, 3H), 3.57 (s, 2H).

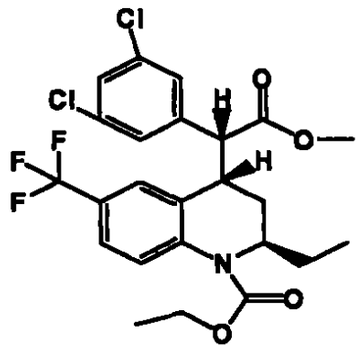
Examples 448, 449, 450 and 451



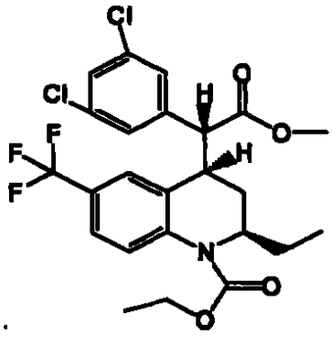
(*R*, *S*, *R*)-4-[(3,5-Dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *R*, *S*)-4-[(3,5-Dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *S*, *S*)-4-[(3,5-Dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *R*, *R*)-4-[(3,5-Dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of methyl (3,5-dichloro)-phenylacetate (311mg, 1.42mmol) in anhydrous N,N-dimethylformamide (3mL) was added sodium hydride (60% mineral oil dispersion, 1.93mmol, 77mg) and the mixture was stirred at room temperature for 30min. A solution of (*R*)-4-bromo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (490mg, mixture of isomers, Preparation 43) in

anhydrous N,N-dimethylformamide (5mL) was added and the mixture was stirred at room temperature for 5min. Water was added and the mixture was extracted with diethyl ether (3 x 20mL) and the organic extract was diluted with heptane and evaporated to dryness to give the crude product as a yellow oil (~460mg). Purification was achieved using radial chromatography (Chromatron model 7924T, Harrison Research, Palo Alto, CA) with a 4mm silica gel rotor eluting with hexanes/ethyl acetate 9:1 and subsequently rechromatographing appropriate fractions eluting with dichloromethane/hexanes 45:55 to give the title compounds:

(*R*, *S*, *R*)-4-[(3,5-dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (10mg);

MS: 518.3 $[M+H]^+$ found;

^{1}H-NMR ($CDCl_3$) δ 7.55 (brd, J=8.30Hz, 1H), 7.49 (brd, J=8.30Hz, 1H), 7.48 (brs, 1H), 7.33 (m, 2H), 7.33 (m, 1H), 4.33 (m, 1H), 4.31 (m, 1H), 4.24 (m, 1H), 3.56 (d, J=11.62Hz, 1H), 3.52 (m, 1H), 3.46 (s, 3H), 1.86 (m, 1H), 1.53 (m, 1H), 1.47 (m, 2H), 1.34 (t, J=7.47Hz, 3H), 0.74 (t, J=7.47Hz, 3H).

(*R*, *R*, *S*)-4-[(3,5-dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (24mg);

MS: 518.3 $[M+H]^+$ found;

^{1}H-NMR ($CDCl_3$) δ 7.52 (m, 1H), 7.50 (m, 1H), 7.35 (t, J=1.66Hz, 1H), 7.32 (brs, 1H), 7.30 (d, J=1.66Hz, 2H), 4.30 (m, 1H), 4.27 (m, 1H), 4.20 (m, 1H), 3.78 (d, J=11.61Hz, 1H), 3.74 (s, 3H), 3.28 (m, 1H), 1.85 (m, 1H), 1.49 (m, 1H), 1.39 (m, 1H), 1.30 (t, J=7.47Hz, 3H), 0.91 (m, 1H), 0.72 (t, J=7.47Hz, 3H).

(*R*, *S*, *S*)-4-[(3,5-dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (29mg);

MS: 518.3 $[M+H]^+$ found;

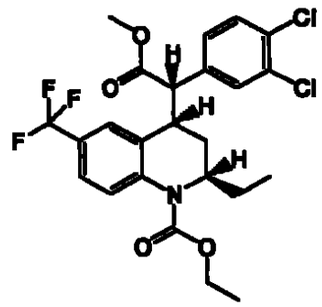
^{1}H-NMR ($CDCl_3$) δ 7.43 (d, J=8.30Hz, 1H), 7.36 (dd, J=8.30, 1.66Hz, 1H), 7.15 (t, J=1.66, 1H), 6.88 (d, J=1.66Hz, 2H), 6.69 (brs, 1H), 4.45 (m, 1H), 4.32 (m, 1H), 4.31 (m, 1H), 3.75 (s, 3H), 3.62 (d, J=10.79Hz, 1H), 3.40 (m, 1H), 2.88 (m, 1H), 1.75 (m, 1H), 1.64 (m, 1H),1.48 (m, 1H), 1.34 (t, J=7.47Hz, 3H), 0.83 (t, J=7.47Hz, 3H).

(*R*, *R*, *R*)-4-[(3,5-dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (18mg);

MS: 518.3 $[M+H]^+$ found;

^{1}H-NMR ($CDCl_3$) δ 7.51 (brd, J=8.59Hz, 1H), 7.43 (brd, J=8.59Hz, 1H), 7.33 (m, 2H), 7.31 (m, 1H), 7.10 (brs, 1H), 4.40 (m, 1H), 4.28 (m, 1H), 4.23 (m, 1H), 4.06 (d, J=10.15Hz, 1H), 3.74 (s, 3H), 3.24 (m, 1H), 2.32 (m, 1H), 1.64 (m, 1H), 1.47 (m, 1H),1.37 (m, 1H), 1.32 (t, J=7.02Hz, 3H), 0.83 (t, J=7.47Hz, 3H).

Example 452



(*R*, *R*, *S*)-4-[(3,4-Dichloro-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

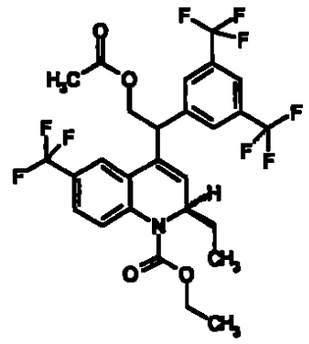
To a solution of methyl (3,4-dichloro)-phenylacetate (1.22gm, 5.57mmol) in anhydrous N,N-dimethylformamide (5mL) was added sodium hydride (60% mineral oil dispersion, 7mmol, 280mg) and the mixture was stirred at room temperature for 5min. A solution of (*R*)-4-bromo-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (798mg, mixture of isomers, Preparation 43) in anhydrous N,N-dimethylformamide (4mL) was added and the mixture was stirred at room temperature for 15min. Water was added and the mixture was acidified by addition of 2N hydrochloric acid then extracted with dichloromethane (x 3) and the organic extract was dried over anhydrous sodium sulfate and evaporated to dryness to give a yellow oil. This was dissolved in tetrahydrofuran (10mL) and water (5mL) and aqueous sodium hydroxide (2N, 10mL) was added. The mixture was stirred at room temperature for 24hr then partitioned between hydrochloric acid (0.1N) and dichloromethane. The organic extract was dried over anhydrous sodium sulfate and evaporated to dryness to give a mixture of carboxylic acids. This material was purified by chromatography on silica gel eluting with hexanes/ethyl acetate 5:1 then 4:1. Fractions containing the first carboxylic acid to elute (with the desired *R*, *R*, *S* stereochemistry) were combined, evaporated to dryness under vacuum and dissolved in methanol (25mL). Trimethylsilyldiazomethane (2M solution in hexanes, Aldrich Chemical Company, Milwaukee, WI) was added slowly until effervescence ceased and a yellow color persisted. This was discharged by addition of a small

amount of acetic acid then the solvent was removed under vacuum and the residue was purified by chromatography on silica gel eluting with a hexanes/dichloromethane gradient from 2:1 to 1:2. Final purification was achieved using reverse phase HPLC using the Shimadzu preparative HPLC system (Shimadzu Corporation, Kyoto, Japan) eluting with a 30-100% acetonitrile/water/0.1% formic acid gradient on a 19x50mm Waters Symmetry Column (Waters Corp, Milford, MA) 8 min run, 6 min gradient, 25mL/min, UV triggered collection, observing at 210nm. The product-containing fractions were evaporated to dryness to give the title compound (75mg).

MS: 518.3 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.52 (m, 1H), 7.51 (m, 1H), 7.50 (m, 1H), 7.47 (d, J=8.3Hz, 1H), 7.34 (brs, 1H), 7.25 (dd, J=8.3, 2.49Hz, 1H), 4.28 (m, 1H), 4.27 (m, 1H), 4.20 (m, 1H), 3.80 (d, J=11.62Hz, 1H), 3.73 (s, 3H), 3.29 (m, 1H), 1.86 (m, 1H), 1.50 (m, 1H), 1.37 (m, 1H), 1.30 (t, J=7.47Hz, 3H), 0.90 (m, 1H), 0.71 (t, J=7.47Hz, 3H).

Example 453

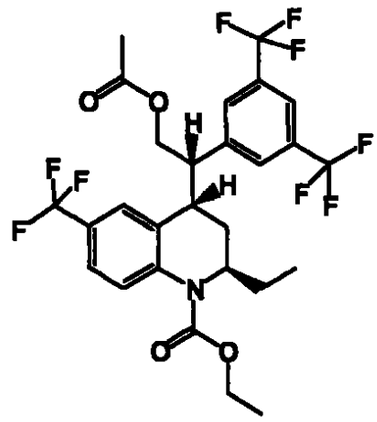


(*R, S*) and (*R, R*)-4-[2-Acetoxy-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of the diastereoisomeric mixture (*R, R*) and (*R, S*)-4-[1-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester (Example 437, 57mg, 0.102mmol) in dichloromethane (1mL) under nitrogen was added triethylamine (43µL, 0.306mmol) followed by acetyl chloride (9µL, 0.132mmol). After 3hr the mixture was partitioned between water and dichloromethane, the organic layer was separated, dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by chromatography on silica gel eluting with hexanes then hexanes/ethyl acetate 19:1 then 9:1 then 4:1 then 3:7 and finally 2:3 to give the title compound as a mixture of diastereoisomers (51mg).

MS: 598.3 $[M+H]^+$ found.

Example 454



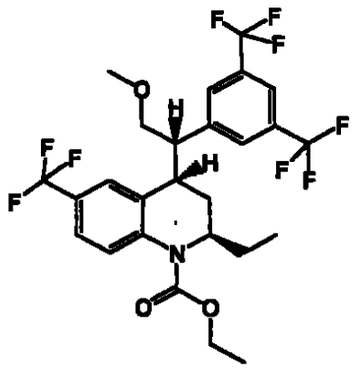
(*R*, *R*, *S*)-4-[2-Acetoxy-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 447, 50mg, 0.0896mmol) in dichloromethane (1mL) under nitrogen was added triethylamine (37µL, 0.269mmol) followed by acetyl chloride (8.3µL, 0.116mmol). After 30min the mixture was partitioned between water and dichloromethane, the organic layer was separated, dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by chromatography on silica gel eluting with hexanes then hexanes/ethyl acetate 19:1 then 9:1 then 4:1 to give the title compound (41mg).

MS: 600.4 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.85 (s, 1H), 7.73 (s, 2H), 7.64 (m, 1H), 7.62 (m, 1H), 4.80 (dd, J=11.62, 4.15Hz, 1H), 4.29 (m, 1H), 4.25 (m, 1H), 4.23 (m, 1H), 4.20 (m, 1H), 3.72 (ddd, J=9.13, 9.13, 3.32Hz, 1H), 2.79 (m, 1H), 1.97 (s, 3H), 1.84 (m, 1H), 1.46 (m, 1H), 1.32 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.87 (m, 1H), 0.69 (t, J=7.47Hz, 3H).

Example 455



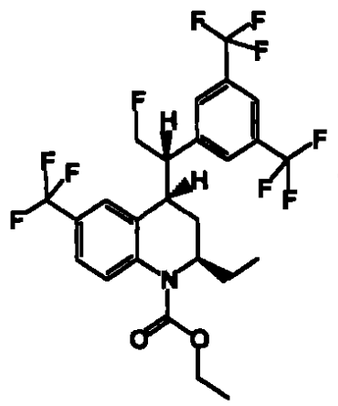
(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-methoxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 447, 20mg, 0.035mmol) in tetrahydrofuran (1mL) under nitrogen was added sodium hydride (60% mineral oil dispersion, 0.043mmol, 1.7mg) followed after 5min by iodomethane (2 drops). After stirring for 16hr additional aliquots of sodium hydride (2mg) and iodomethane (3 drops) were added. The mixture was stirred at room temperature for 48hr then diluted with ethyl acetate. The mixture was washed with water, the organic layer separated, dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was purified by chromatography on silica gel eluting with hexanes then hexanes/ethyl acetate 19:1 then 9:1 to give the title compound (19mg).

MS: 572.5 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.81 (s, 1H), 7.76 (s, 2H), 7.61 (brs, 1H), 7.52 (m, 2H), 4.27 (m, 1H), 4.24 (m, 1H), 4.21 (m, 1H), 3.89 (dd, J=9.96, 3.32Hz, 1H), 3.74 (dd, J=9.13, 7.47Hz, 1H), 3.55 (m, 1H), 3.29 (s, 3H), 2.85 (m, 1H), 1.80 (m, 1H), 1.47 (m, 1H), 1.32 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.87 (m, 1H), 0.69 (t, J=7.47Hz, 3H).

Example 456



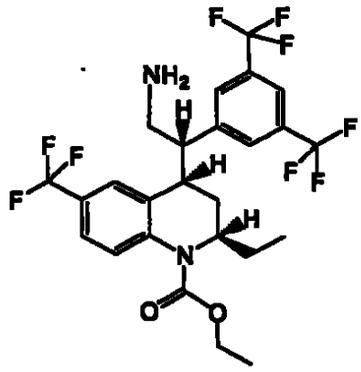
(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-fluoro-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 447, 20mg, 0.035mmol) in dichloromethane (1mL) under nitrogen was added diethylaminosulfur trifluoride (47µL, 0.358mmol). The mixture was stirred at room temperature for 3hr then a further aliquot of diethylaminosulfur trifluoride (47µL, 0.358mmol) was added. After 1hr the mixture was partitioned between water and dichloromethane, the organic layer was separated, dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was initially purified by chromatography on silica gel eluting with hexanes/ethyl acetate 19:1 then 18:1 then 9:1 and finally purified by reverse phase hplc using the Shimadzu preparative HPLC system (Shimadzu Corporation, Kyoto, Japan) eluting with a 30-100% acetonitrile/water/0.1% formic acid gradient on a 19x50mm Waters Symmetry Column (Waters Corp, Milford, MA) 8 min run, 6 min gradient, 25mL/min, UV triggered collection, observing at 210nm. The product-containing fractions were evaporated to dryness to give the title compound (3mg).

MS: 560.3 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.80 (s, 2H), 7.55 (m, 2H), 7.54 (s, 1H), 4.93 (ddd, J=48.47, 9.96, 4.14Hz, 1H), 4.82 (ddd, J=48.47, 9.96, 6.64Hz, 1H), 4.28 (m, 1H), 4.27 (m, 1H), 4.23 (m, 1H), 3.72 (m, 1H), 2.91 (m, 1H), 1.88 (m, 1H), 1.48 (m, 1H), 1.34 (m, 1H), 1.32 (t, J=7.47Hz, 3H), 0.92 (m, 1H), 0.71 (t, J=7.47Hz, 3H).

Example 457



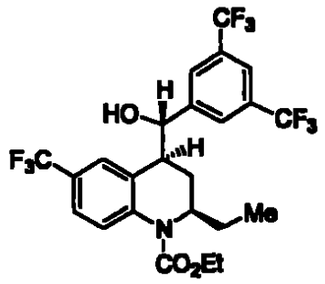
(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-amino-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 438, 25mg, 0.0438mmol) in tetrahydrofuran (3mL) under nitrogen was added borane-dimethylsulfide complex (8.3µL, 0.0876mmol). The mixture was heated at 70°C for 48hr then water (2.5mL) and saturated aqueous sodium carbonate solution (1mL) was added. The mixture was heated at 70°C for 1hr then partitioned between water and dichloromethane. The organic layer was evaporated to dryness under vacuum and the residue dissolved in diethyl ether (5mL) and 2N hydrochloric acid (1mL) added. After 24hr the mixture was diluted with water, sodium carbonate solution added and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. The crude product was purified by chromatography on silica gel eluting with hexanes/ethyl acetate 3:1 then ethyl acetate give the title compound (18.5mg).

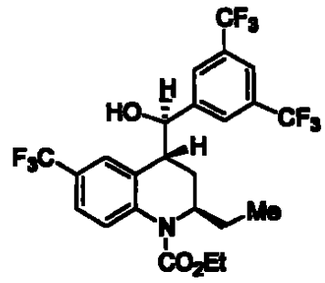
MS: 557.4 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.77 (s, 2H), 7.58 (brs, 1H), 7.52 (m, 2H), 4.27 (m, 1H), 4.23 (m, 1H), 4.22 (m, 1H), 3.44 (dd, J=13.28, 3.32Hz, 1H), 3.35 (m, 1H), 3.09 (dd, J=13.28, 9.13Hz, 1H), 2.76 (m, 1H), 1.76 (m, 1H), 1.45 (m, 1H), 1.34 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.84 (m, 1H), 0.69 (t, J=7.47Hz, 3H).

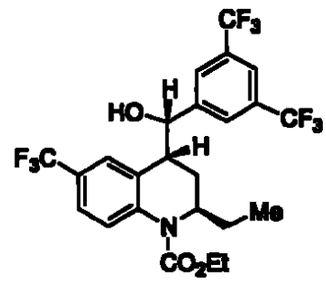
Examples 458, 459, 460 and 461



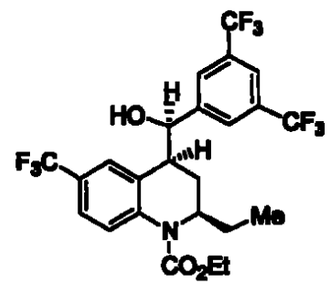
[(*R*, *S*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester



[(*R*, *R*, *R*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester



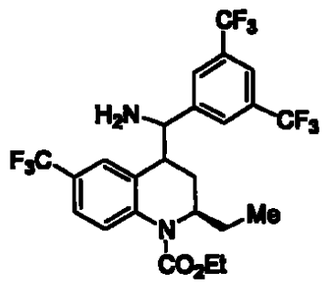
[(*R*, *R*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester



[(*R*, *S*, *R*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

These compounds (previously prepared in Examples 22, 23, 24 and 25) were prepared in optically enriched form by resolution of the corresponding racemate indicated, or an intermediate in its synthesis, using methods analogous to those described herein.

Examples 462, 463, 464 and 465



Preparation of [(*R*, *R*, *R*)], [(*R*, *R*, *S*)], [(*R*, *S*, *S*)], and [(*R*, *S*, *R*)]-4-[Amino-(3,5-bis-trifluoromethyl-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

General procedure to make amine compounds: [(*R*, *R*, *R*)]-4-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.527 grams, 0.971 mmol, 1 eq) was placed in a round bottomed flask equipped with a magnetic stir bar. Methylene chloride (20 mL) was added followed by the addition of triethylamine (0.456 mL, 3.37 mmol, 3.37 eq) and mesyl chloride (0.150 mL, 1.94 mmol, 2.0 eq) at room temperature and the reaction mixture was stirred overnight. The reaction mixture was quenched with water, extracted 4 times with ethyl acetate. The organic layer was washed with 0.1M HCl, followed by saturated bicarbonate solution and dried over sodium sulfate. The solution was filtered, concentrated and dried on the high vacuum to provide [(*R*, *R*, *R*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-methanesulfonyloxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.599 grams, 99% yield) as a white solid, MS (ES+) m/z=622 (M+1).

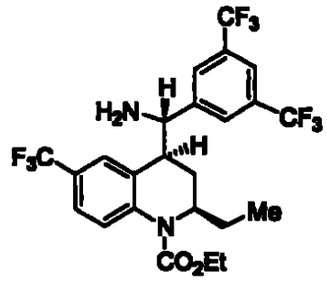
[(*R*, *R*, *R*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-methanesulfonyloxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.313 grams, 0.504 mmol, 1 eq) was placed in a round bottomed flask equipped with a magnetic stir bar. DMF (12 mL) was added followed by the addition of sodium azide (0.201 grams, 0.3.10 mmol, 6.1 eq). The reaction mixture was heated to 70°C for 12 hours. The reaction mixture was cooled to room temperature, diluted into 200 mL of

EtOAc and washed 4 times with brine and water. The EtOAc was collected, dried over sodium sulfate, filtered and concentrated. The material was purified on a Biotage flash 40s to provide [(*R, R, S*)]-4-[Azido-(3,5-bis-trifluoromethyl-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester 0.202 grams, 71% yield) MS (ES+) m/z=569 (M+1).

[(*R, R, S*)]-4-[Azido-(3,5-bis-trifluoromethyl-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.202 grams, 0.356 mol, 1 eq) was placed in a round bottomed flask and equipped with a magnetic stir bar and reflux condenser. NH_4CO_2H (0.226 grams, 3.58 mol, 10.1 eq) and Pd/C (0.113 grams, 0.107 mol, 0.30 eq) was added followed by the addition of a 2:1 solution of methanol and ethyl acetate (8.80 mL). The reaction mixture was refluxed for 2 hours and then filtered through Celite®. The filtrate was concentrated but not to dryness and partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was collected, dried over sodium sulfate, filtered and concentrated. The crude material was purified on Biotage Flash 40 M to provide the desired compound, [(*R, R, S*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.162 grams, 83% yield) MS (ES+) m/z=543 (M+1).

^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H), 1.32 (t, 3H), 1.34-1.57 (m, 3H), 2.53 (m, 1H), 3.00 (m, 1H), 4.28 (q, 2H), 4.50 (d, 1H), 4.54 (m, 1H), 7.03 (s, 1H), 7.42 (d, 1H), 7.60 (d, 1H), 7.66 (s, 2H), 7.72 (s, 1H).
MS (ES+) m/z=543 (M+1).

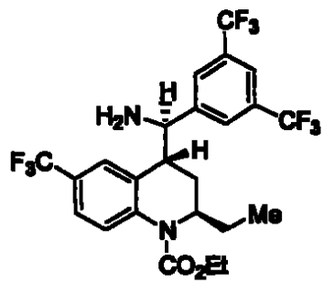
These additional compounds were prepared using analogous procedures to those described herein:



[(*R, S, S*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester:

^{1}H NMR ($CDCl_3$): δ 0.71 (t, 3H), 1.00 (m, 1H), 1.29 (t, 3H), 1.33-1.52 (m, 2H), 1.67 (m, 1H & H_2O), 2.70 (m, 1H), 4.15-4.31 (m, 3H), 4.47 (d, 1H), 7.51 (m, 2H), 7.84 (s, 1H), 7.89 (s, 2H), 7.91 (s, 1H);

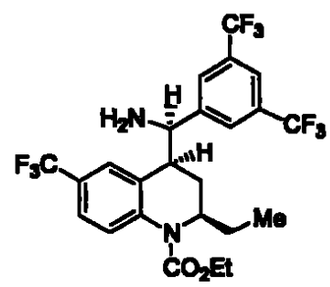
MS (ES+) m/z=543 (M+1).



[(*R*, *R*, *R*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester:

HNMR ($CDCl_3$): δ 0.75 (t, 3H), 1.33 (t, 3H), 1.37-1.62 (m, 3H), 1.82 (m, 1H), 2.98 (m, 1H), 4.17-4.36 (m, 4H), 7.51 (s, 1H), 7.53-7.61 (m, 2H), 7.83 (s, 1H), 7.86 (s, 2H);

MS (ES+) m/z=543 (M+1).



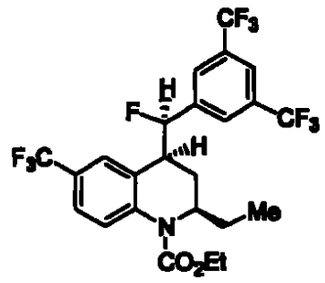
[(*R*, *S*, *R*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-ethyl-6-2-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester:

HNMR ($CDCl_3$): δ 0.82 (t, 3H), 1.27 (t, 3H), 1.40-1.64 (m, 3H), 2.07 (m, 1H), 2.76 (m, 1H), 4.09-4.27 (m, 3H), 5.07 (m, 1H), 7.55 (q, 2H), 7.66 (s, 1H), 7.83 (s, 1H), 7.96 (s, 2H);

MS (ES+) m/z=543 (M+1).

Example 466, 467, 468 and 469

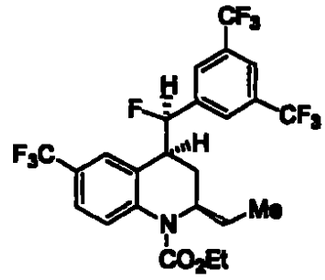
The following compounds were prepared from starting materials and procedures analogous to those described above, particularly in Examples 18, 19, and 456.



[(*R, S, R*)]-4-(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 7.92 (s, 1H), 7.83 (s, 2H), 7.67 (s, 1H), 7.57 (s, 2H), 6.5 (d, 1H), 4.24 (m, 3H), 2.91(dd, 1H), 2.08 (m, 1H), 1.51 (m, 3H), 1.27 (t, 3H), 0.80 (t, 3H);

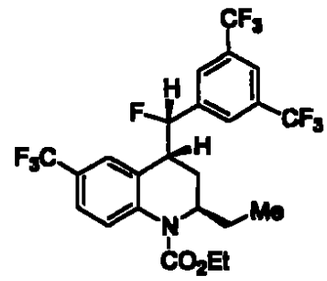
MS: 546.3 [M+H]+ found.



[(*R, S, S*)]-4-(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.88 (s, 2H), 7.76 (s, 1H), 7.55 (s, t, 2H), 5.88 (dd, J=9.13 Hz, 1H), 4.25 (m, 3H), 3.10 (m, 1H), 1.75 (m, 1H), 1.47 (m, 2H), 1.29 (t, 3H), 1.18 (t , 3H), 0.77 (t, 3H);

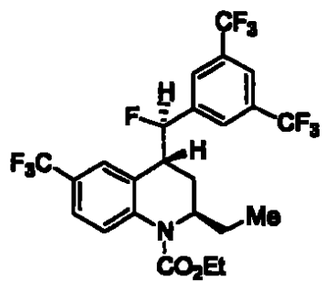
MS: 546.4 [M+H]+ found.



[(*R, R, S*)]-4-(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 7.8 (s, 1H), 7.59 (d, 1H), 7.47 (d, 1H), 7.43 (s, 2H), 6.86 (s, 1H), 5.65 (dd, J=7.88 Hz, 1H), 4.60 (m, 1H), 4.28 (m, 2H), 3.21 (m, 1H), 2.65 (m, 3H), 1.74 (m, 1H), 1.41-1.62 (m, 2H), 1.31 (t, 3H), 0.86 (t, 3H);

MS: 546.3 [M+H]+ found



[(*R*, *R*, *R*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H-NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.83 (s, d, 3H), 7.52 (d, 1H), 7.41(s, 1H), 5.58 (dd, J=7.47 Hz, 1H), 4.42 (m, 1H), 4.24 (m, 2H), 3.40 (m, 1H), 1.97 (m, 1H), 1.74 (m, 1H), 1.41 (m, 2H), 1.27 (t, 3H), 0.79 (t , 3H);

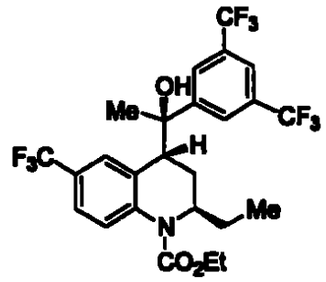
MS: 546.3 [M+H]+ found.

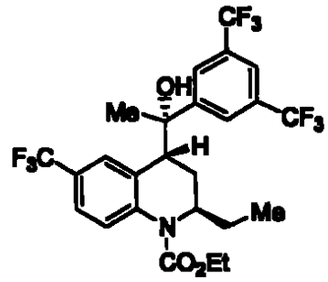
Examples 470, 471, 472 and 473

The following compounds were prepared from starting materials and procedures analogous to those described above, as shown in Scheme 2 whereby the addition of a suitable organometallic derivative such as magnesium or lithium derivative, prepared from a compound alkyl-Hal, wherein Hal represents a chlorine, bromine or iodine atom to XXV produced compounds shown in examples 470, 471, 472 and 473.

[(*R*,*R*), (*S*,*S*)]-4-[(3,5-Bis-trifluoromethyl-benzoyl)]-6,-trifluoromethyl -2-ethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (0.015 grams, 0.028 mmol) was placed in a small round bottomed flask containing a magnetic stir bar and dissolved in 0.50 mL of tetrahydrofuran. Methyl magnesium bromide solution (0.028 mL of 3.0 M in diethylether) was added to the reaction mixture at room temperature and stirred for 2 hours. The reaction mixture was then quenched with saturated ammonium chloride solution and extracted into ethyl acetate. The organic layer was washed with water, dried over magnesium sulafte, filtered and concentrated to provide the desired products as an crude oil. The alcohol diastereomers were separated by silica gel chromatography to provide [(*R*, *R*, *R*)],-4-[(3,5-bis-

trifluoromethyl-phenyl)-1-hydroxyl- ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester and [(*R*, *R*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-1-hydroxyl- ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester.





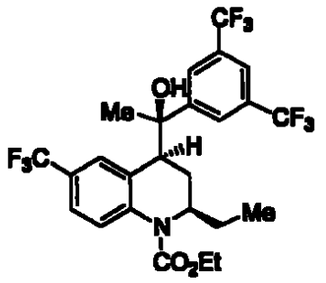
[(*R*, *R*, *R*)], (*R*, *R*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-1-hydroxyl- ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

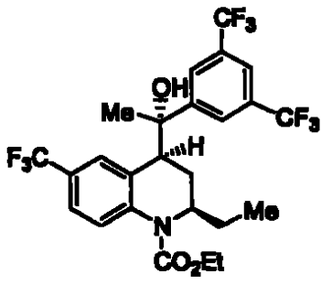
First eluting compound: ^{1}H-NMR ($CDCl_3$): δ 7.86 (s, 2H), 7.80 (s, 1H), 7.53 (dd, 2H), 7.34 (s, 1H), 4.3 (m, 2H), 4.18 (m, 1H), 3.18 (m, 1H), 1.95 (m, 1H), 1.80 (s, 1H), 1.5-1.63 (m, 4H), 1.24 - 1.45 (m, 5H), 0.70 (t, 3H);

MS: 588.3 [M+H]+ found.

Second eluting compound:^{1}H-NMR ($CDCl_3$): δ 7.76 (m, 3H), 7.53 (d, 1H), 7.42 (d, 1H), 7.06 (s, 1H), 4.41 (m, 1H), 4.2 (q, 2H), 3.18 (m, 1H), 2.30 (m, 1H), 1.91 (br s, 1H), 1.62-1.74 (m, 4H), 1.24 - 1.43 (m, 5H), 0.77 (t, 3H);

MS: 588.3 [M+H]+ found.





[(*R*, *S*, *R*)], (*R*, *S*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-1-hydroxyl- ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

First eluting compound: ^{1}H-NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.55 (m ,2H), 7.35 (s, 1H), 4.3 (m, 2H), 4.19 (m, 1H), 3.20 (m, 1H), 1.91 (m, 1H), 1.60 (s, 3H), 1.30 (t, 3H), 0.70 (t, 3H);

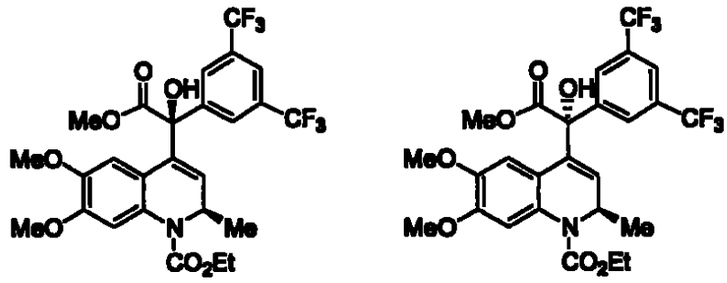
MS: 556.2 [M-H]$^-$ found.

Second eluting compound:^{1}H-NMR ($CDCl_3$): δ 8.0 (s, 2H), 7.80 (s, 1H), 7.50 (brs, 1H), 7.40 (dd, 2H), 4.4 (br m, 1H), 4.20 (m, 2H), 3.05 (d, 1H), 2.55 (br m, 1H), 1.74 (s, 3H), 1.63 (m, 1H), 1.43 (m, 2H), 1.30 (t, 3H), 0.90 (t, 3H);

MS: 558.3 $[M+H]^+$ found.

Example 474 and 475

The following compounds were prepared from starting materials and procedures analogous to those described in Scheme 1 above, particularly in Example 2.



[(*R*, *R*)], (*R*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-1-hydroxyl-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl-2*H*-quinoline-1-carboxylic acid ethyl ester

Diastereomer 1: ^{1}H-NMR ($CDCl_3$): δ 7.92 (s, 2H), 7.73 (s, 1H), 6.81 (s, 1H), 5.80 (d, 1H), 5.20 (br m, 1H), 4.40 (brs, 1H), 4.30 (m, 1H), 4.20 (br m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.50 (s, 3H), 1.34 (m, 4H), 1.09 (d, 3H);

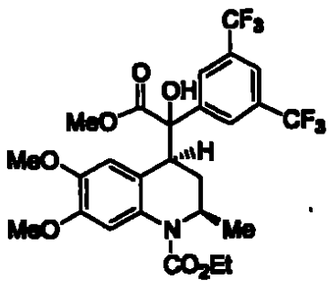
MS: 578.5 [M+H]+ found.

Diastereomer 2: ^{1}H-NMR ($CDCl_3$): δ 8.18 (s, 2H), 7.87 (s, 1H), 6.67 (s, 1H), 5.65 (br s, 1H), 5.15 (br s, 1H), 4.31 (brm, 1H), 4.20 (br m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 1.33 (t, 3H), 1.09 (d, 3H);

MS: 578.6 [M+H]+ found.

Examples 476 and 477

The following compounds were prepared from starting materials and procedures analogous to those described in Scheme 1 above, particularly in Examples 7 and 8.



[(*R*, *S*, *R*), (*R*, *S*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl- methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

First Eluting: ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 2H), 7.88 (s, 1H), 7.03 (br s, 1H), 6.73 (s, 1H), 4.31 (m, 1H), 4.20 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.30 (d, 1H), 1.70 (m, 2H), 1.21 –1.30 (t, m, 4H), 1.09 (d, 3H);

MS: 580.6 [M+H]+ found.

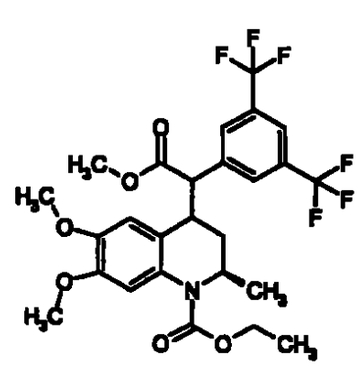
Second Eluting: ^{1}H NMR ($CDCl_3$): δ 8.25 (s, 2H), 7.84 (s, 1H), 6.82 (br s, 1H), 6.30 (s, 1H), 4.55 (m, 1H), 4.30 (m, 1H), 4.20 (m, 1H), 3.88 (s, 3H), 3.80 (s, 3H) 3.60 (d, 1H), 3.40 (s, 3H), 2.03 (m, 2H), 1.55 (m, 1H), 1.32 (t, 3H) 1.09 (d, 3H);

MS: 580.5 [M+H]+ found.

Examples 478 and 479

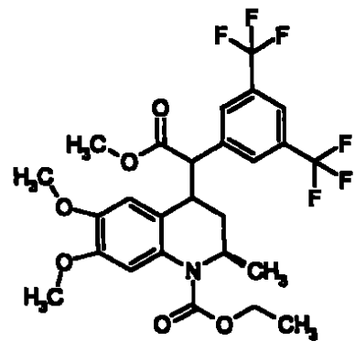
The following compounds were prepared from starting materials and procedures analogous to those described above, particularly in Examples 448, 449, 450 and 451.

[(*R*, *R*, *R*)], (*R*, *R*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester



^{1}H NMR ($CDCl_3$): δ 7.97 (s, 2H), 7.83 (s, 1H), 7.0 (brs, 1H), 6.20 (s, 1H), 4.50 (m, 1H), 4.30 (m, 1H), 4.30 (m, 1H), 4.19 (m, 1H), 4.17 (d, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.51 (s, 3H), 3.32 (m, 1H), 2.30 (m, 1H), 1.31 (t, 3H), 1.20 (d, 3H);

MS: 564.5 [M+H]+ found.



^{1}H NMR ($CDCl_3$): δ 7.87 (s, 3H), 7.03 (br s, 1H), 6.72 (s, 1H), 4.31 (m, 2H), 4.20 (m, 1H), 3.98 (d, 1H), 3.86 (s, 6H), 3.75 (s, 3H), 3.32 (t, 1H), 1.70 (m, 1H), 1.30 (t, 3H), 1.07 (d, 3H), 0.80 (m, 1H);

MS: 564.4 [M+H]+ found.

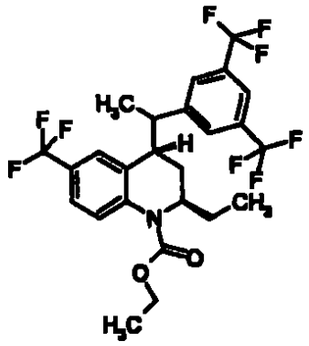
Example 480

The following compound was prepared from starting materials and procedures analogous to those described above, particularly in Examples 470, 471, 472 and 473.

[(*R*, *R*, *R*)], (*R*, *R*, *S*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-1-hydroxyl- ethyl]-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.079 grams, 0.142 mmol) was placed in a small round bottomed flask containing a magnetic stir bar and dissolved in 1.5 mL of anhydrous chloroform. To this reaction solution, 2,6-di-t-butyl-4-methylpyridine (0.117 grams, 0.568 mmol) and thionyl chloride (0.051 grams, 0.425 mmol) was added and allowed to stir at room temperature for four hours. The reaction mixture was quenched with water and extracted into methylene chloride. The organic layers was washed with 0.1 N HCl, dried over magnesium sulfate, filtered and concentrated to provide [(*R*, *R*, *R*)], (*R*, *R*, *S*)]-4-[1-(3,5-bis-trifluoromethyl-phenyl)-1-chloro-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester as an oil which was used without further purification. [(*R*, *R*, *R*)], (*R*, *R*, *S*)]-4-[1-(3,5-bis-trifluoromethyl-phenyl)-1-chloro-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.085 grams, 0.142 mmol) was placed in a small round bottomed flask

containing a magnetic stir bar and dissolved in 0.48 mL THF. This solution was added glacial acetic acid (0.48 mmol), HCl (0.80 mmol), and zinc dust ((0.093 grams, 1.42 mmol). The reaction mixture was stirred at room temperature for three hours. The reaction mixture was quenched with water and extracted three times with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, filtered and concentrated to provide [(*R, R*)-4-[1-(3,5-bis-trifluoromethyl-phenyl)-vinyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester as an oil.

[(*R,R*)-4-[1-(3,5-bis-trifluoromethyl-phenyl)-vinyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (15 mg) was placed in a small round bottomed flask and dissolved in 10 mL of methanol. To this solution was added 10 mg of 10% Pd/C. The reaction mixture was hydrogenated at 45 psi for 12 hours. The reaction mixture was then filtered through Celite® and washed with methanol. The filtrate was concentrated to an oil and purified by silica gel chromatography to provide [(*R, R, R*)], (*R, R, S*)]-4-[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]- 6,7-trifluoromethyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester in 66% yield.

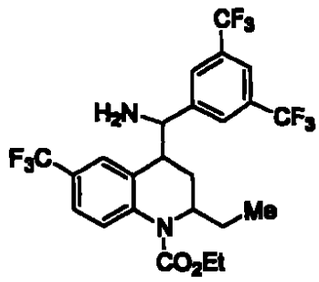


[(*R, S, R*)], (*R, S, S*)]-4-[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl- 6,7-trifluoromethyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester

^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.65 (s, 2H), 7.59 (dd, 2H), 7.41 (s, 1H), 4.30 (m, 1H), 4.20 (m, 2H), 2.95 (m, 2H), 1.80 (m, 1H), 1.58 (m, 2H), 1.40 (m, 1H), 1.30 (t, 3H), 1.20 (d, 3H), 0.72 (t, 3H);

MS: 542.3 [M+H]+ found.

Example 481 (Stereo-isomers of Examples 462, 463, 464 and 465)



[(*S*, *R*, *S*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

[(*S*, *S*, *S*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

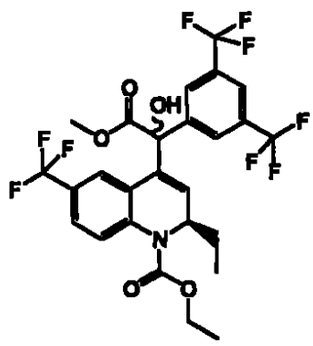
[(*S*, *R*, *R*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

[(*S*, *S*, *R*)], 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt of said compound.

The above stereo-isomers of examples 462, 463, 464 and 465 are prophetic and may be prepared in optically enriched form by resolution of the corresponding racemate indicated, or an intermediate in its synthesis, using methods analogous to those described herein.

Examples 462 and 463



(*R*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester

The mixture of two diastereoisomers (Example 2, 1.0g) was chromatographed on silica (Flash 40M column, Biotage, Dyar Corp., Charlottesville,

VA) eluting with a methylene chloride -hexanes gradient from 2:3 to 4:1 to give the title compounds as white solids.

First eluting diastereoisomer (4a stereochemistry not determined):

MS: 597.9 $[M-H]^-$ found

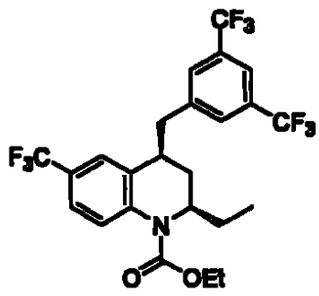
^{1}H-NMR ($CDCl_3$) δ 7.92 (s, 2H), 7.75 (s, 1H), 7.67 (s, 1H), 7.65 (d, J=8.30Hz, 1H), 7.34 (dd, J=8.30, 1.66Hz, 1H), 5.97 (d, J=6.64Hz, 1H), 5.04 (m, 1H), 4.53 (s, 1H), 4.27 (m, 2H), 3.87 (s, 3H), 1.47 (m, 1H), 1.35 (m, 1H), 1.28 (t, J=7.47Hz, 3H), 0.85 (d, J=6.64Hz, 3H).

Second eluting diastereoisomer (4a stereochemistry not determined):

MS: 597.9 $[M-H]^-$ found

^{1}H-NMR ($CDCl_3$) δ 8.16 (s, 2H), 7.90 (s, 1H), 7.65 (d, J=8.30, 1H), 7.63 (s, 1H), 7.45 (dd, J=8.30, 1.66Hz, 1H), 5.82 (d, J=6.42Hz, 1H), 4.96 (m, 1H), 4.34 (s, 1H), 4.27 (m, 2H), 3.78 (s, 3H), 1.47 (m, 1H), 1.35 (m, 1H), 1.33 (t, J=7.47Hz, 3H), 0.83 (d, J=7.47Hz, 3H).

Example 484



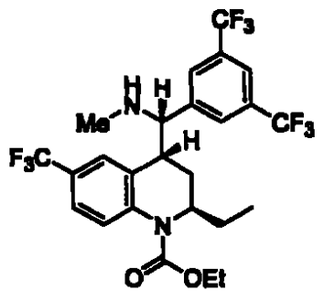
(*R*, *R*)- 4-(3,5-bis-trifluoromethyl-benzyl)-2-ethyl-6-trifluoromethyl-3, 4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

[(*R*, *R*, *R*)]-4-[(3,5-bis-trifluoromethyl-phenyl)-methanesulfonyloxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.045 mmol, 0.0278 g) was placed in a 5 mL reaction flask. To this 1.3 mL of DMF followed by sodium borohydride (0.526 mmol, 0.019 g) was added. The reaction was heated to 85 °C for twelve hours. The reaction mixture was then diluted with ethyl acetate and washed with an aqueous brine solution. The organic layer was collected, dried over sodium sulfate, filtered and concentrated to dryness. The crude reaction mixture was purified on silica gel chromatography to provide 18.5 mg of the desired product

(*R*, *R*)- 4-(3,5-bis-trifluoromethyl-benzyl)-2-ethyl-6-trifluoromethyl-3, 4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in 78% yield.

^{1}H NMR ($CDCl_3$): 0.80 ppm (t, 3H), 1.10 (m, 1H), 1.29 (t, 3H), 1.41-1.62 (m, 2H & H_2O), 2.16 (m, 1H), 2.76-2.87 (m, 2H), 3.64 (d, 1H), 4.15-4.32 (m, 3H), 7.47 (s, 1H), 7.51-7.57 (m, 2H), 7.70 (s, 2H), 7.80 (s, 1H).
MS (ES+) m/z=528 (M+1).

Example 485



(*R*, *R*, *S*) 4-[(3,5-bis-trifluoromethyl-phenyl)-methylaminomethyl]-2-ethyl-6-trifluoromethyl-3, 4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

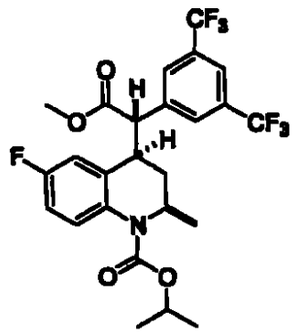
(*R*, *R*, *S*) 4-[Amino-(3,5-bis-trifluoromethyl-phenyl)-methyl]-2-ethyl-6-trifluoromethyl-3, 4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester (0.193 g, 0.357 mmol) was placed in a sealed tube that contained 7 mL of ethyl formate. The tube was sealed and heated for twelve hours at 100 °C. The reaction mixture was then concentrated and purified on silica gel chromatography to provide 0.165 g of the formamide in 81% yield. This product was then placed in a round bottomed flask equipped with a magnetic stir bar and dissolved in 7.3 mL of toluene. To this solution, 2.92 mL of borane methyl sulfide complex in toluene (2.0 M) was added. A *reflux* condenser was attached to the flask and the reaction was heated to 74 °C for twelve hours. The reaction mixture was then quenched with methanol and a few drops of HCl. This mixture was then heated for 1 hour. After cooling to room temperature, the mixture was quenched with aqueous $NaHCO_3$ and extracted 3 times with ethyl acetate. The organics were collected, dried over sodium sulfate and concentrated to dryness. The crude oil was purified on silica gel chromatography to provide (*R*, *R*, *S*) 4-[(3,5-bis-trifluoromethyl-phenyl)-methylaminomethyl]-2-ethyl-6-trifluoromethyl-3, 4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in 41% yield.

^{1}H NMR ($CDCl_3$): 0.81 ppm (t, 3H), 1.33 (t, 3H), 1.36-1.52 (m, 3H), 2.25 (s, 3H), 2.52 (m, 1H), 2.97 (m, 1H), 3.99 (d, 1H), 4.26 (m, 2H), 4.52 (m, 1H), 7.04 (s, 1H), 7.41 (m, 1H), 7.59-7.61 (m, 3H), 7.72 (s, 1H).
MS (ES+) m/z=557 (M+1).

Examples 486 - 499

These compounds were prepared from appropriate starting materials procedures analogous to those described in Examples 9, 10, 433, 434, 438, 443, 444, 452, 454, 457 and described generally in Scheme 2. The appropriately substituted bromo intermediates designated as Formula XVII in Scheme 2, were prepared using procedures described by Matsugi in *Tetrahedron Lett* 2000, *41*, 8523 and Hardy in U.S. patent 6,288,075.

Example 486

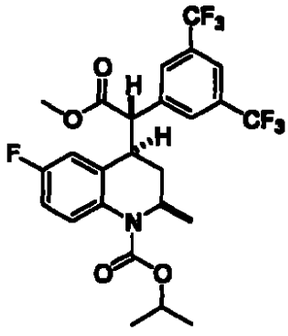


(*RS, RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-6-fluoro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

GCMS (EI): 535 (M+)

^{1}H-NMR ($CDCl_3$): δ 0.87 (m, 1H), 1.04 (d, 3H), 1.25 (m, 3H), 1.32 (d, 3H), 1.69 (m, 1H), 3.33 (m, 1H), 3.76 (s, 3H), 3.92 (d, 1H), 4.29 (m, 1H), 5.03 (m, 1H), 6.81 (dd, 1H), 6.87 (m, 1H), 7.38 (bs, 1H), 7.85 (s, 2H), 7.87 (s, 1H).

Example 487

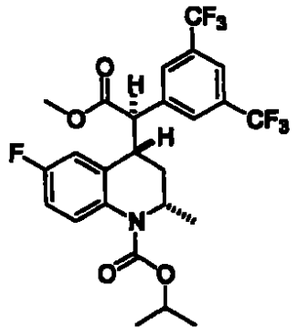


(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-6-fluoro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

GCMS (EI): 535 (M+)

^{1}H-NMR ($CDCl_3$): δ 0.83 (m, 1H), 1.04 (d, 3H), 1.26 (d, 3H), 1.32 (d, 3H), 1.72 (m, 1H), 3.33 (m, 1H), 3.77 (s, 3H), 3.91 (d, 1H), 4.28 (m, 1H), 5.03 (m, 1H), 6.82 (dd, 1H), 6.95 (m, 1H), 7.38 (bs, 1H), 7.84 (s, 2H), 7.87 (s, 1H).

Example 488

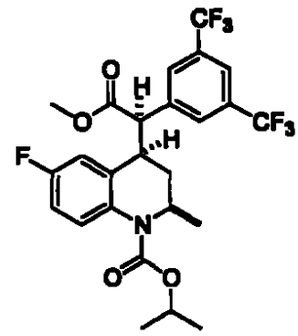


(*S, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-6-fluoro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

GCMS (EI): 535 (M+)

^{1}H-NMR ($CDCl_3$): δ 0.83 (m, 1H), 1.04 (d, 3H), 1.26 (d, 3H), 1.32 (d, 3H), 1.69 (m, 1H), 3.33 (m, 1H), 3.77 (s, 3H), 3.91 (d, 1H), 4.28 (m, 1H), 5.03 (m, 1H), 6.82 (dd, 1H), 6.95 (m, 1H), 7.38 (bs, 1H), 7.84 (s, 2H), 7.87 (s, 1H).

Example 489

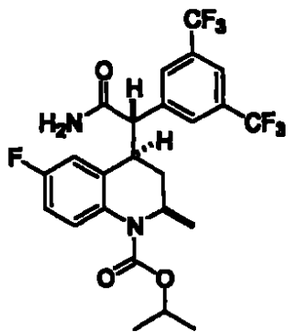


(*RS, RS, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-6-fluoro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

GCMS (EI): 535 (M+)

^{1}H-NMR ($CDCl_3$): δ 0.87 (m, 1H), 1.17 (d, 3H), 1.26 (m, 3H), 1.32 (d, 3H), 2.31 (m, 1H), 3.28 (m, 1H), 3.74 (s, 3H), 4.17 (d, 1H), 4.46 (m, 1H), 5.04 (m, 1H), 6.44 (dd, 1H), 6.87 (m, 1H), 7.38 (m, 1H), 7.84 (s, 1H), 7.89 (s, 2H).

Example 490

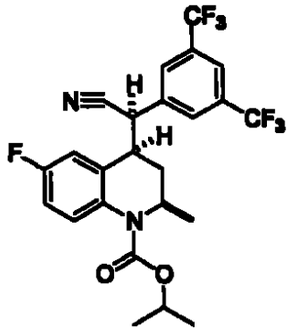


(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-6-fluoro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

GCMS (EI): 520 (M+)

^{1}H-NMR ($CDCl_3$): δ 0.85 (m, 1H), 1.05 (d, 3H), 1.25 (d, 3H), 1.30 (d, 3H), 1.64 (m, 1H), 3.36 (m, 1H), 3.71 (d, 1H), 4.26 (m, 1H), 5.01 (m, 1H), 5.53 (bs, 1H), 5.78 (bs, 1H), 6.93 (m, 2H), 7.37 (m, 1H), 7.85 (s, 2H), 7.87 (s, 1H).

Example 491

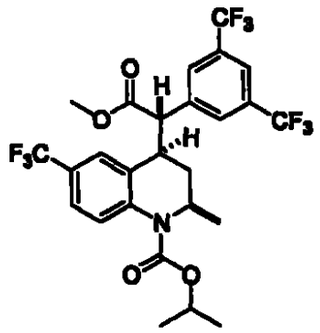


(*RS, RS, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-6-fluoro-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

LCMS (ESI+): 503 (MH+)

^{1}H-NMR ($CDCl_3$): δ 1.19 (d, 3H), 1.24 (d, 3H), 1.28 (d, 3H), 1.45 (m, 1H), 2.18 (m, 1H), 2.87 (m, 1H), 4.31 (m, 1H), 4.77 (d, 1H), 4.99 (m, 1H), 7.04 (bs, 1H), 7.06 (bs, 1H), 7.45 (m, 1H), 7.90 (s, 2H), 7.96 (s, 1H).

Example 492

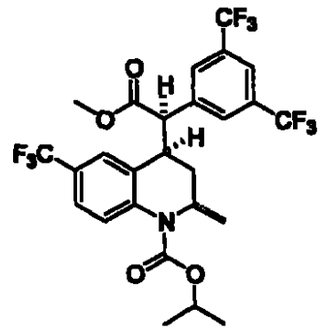


(*RS, RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

GCMS (EI): 585 (M+)

^{1}H-NMR ($CDCl_3$): δ 0.91 (m, 1H), 1.09 (d, 3H), 1.29 (d, 3H), 1.34 (d, 3H), 1.75 (m, 1H), 3.38 (t, 1H), 3.77 (s, 3H), 4.02 (d, 1H), 4.31 (m, 1H), 5.08 (m, 1H), 7.38 (s, 1H), 7.55 (m, 2H), 7.88 (bs, 3H).

Example 493

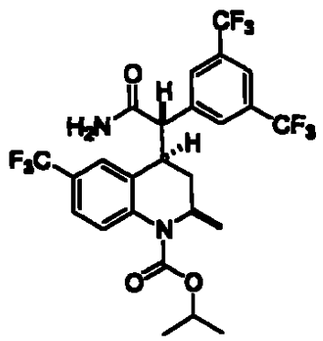


(*RS, RS, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

LCMS (ESI+): 585 (M+)

^{1}H-NMR ($CDCl_3$): δ 1.22 (d, 3H), 1.28 (d, 3H), 1.33 (d, 3H), 1.39 (m, 1H), 2.36 (m, 1H), 3.27 (m, 1H), 3.76 (s, 3H), 4.27 (d, 1H), 4.46 (m, 1H), 5.06 (m, 1H), 7.08 (s, 1H), 7.43 (d, 1H), 7.57 (d, 1H), 7.85 (s, 1H), 7.93 (s, 2H).

Example 494

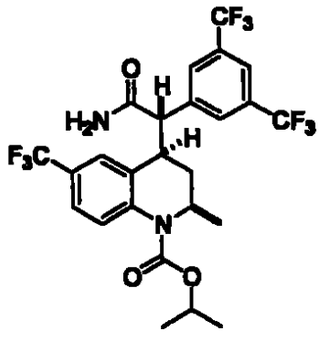


(*RS, RS, SR*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

LCMS (ESI+): 571 (MH+)

^{1}H-NMR ($CDCl_3$): δ 0.91 (m, 1H), 1.09 (d, 3H), 1.27 (d, 3H), 1.33 (d, 3H), 1.68 (m, 1H), 3.46 (t, 1H), 3.81 (d, 1H), 4.28 (m, 1H), 5.04 (m,1H), 5.54 (bs, 1H), 5.82 (bs, 1H), 7.46 (s, 1H), 7.50 (d, 1H), 7.56 (d, 1H), 7.88 (s, 3H).

Example 495

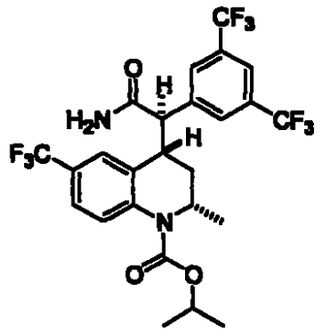


(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

LCMS (ESI+): 571 (MH+)

^{1}H-NMR ($CDCl_3$): δ 0.87 (m, 1H), 1.09 (d, 3H), 1.26 (d, 3H), 1.33 (d, 3H), 1.69 (m, 1H), 3.45 (t, 1H), 3.83 (d, 1H), 4.27 (m, 1H), 5.03 (m,1H), 5.65 (bs, 1H), 5.99 (bs, 1H), 7.46 (s, 1H), 7.49 (d, 1H), 7.55 (d, 1H), 7.88 (s, 3H).

Example 496

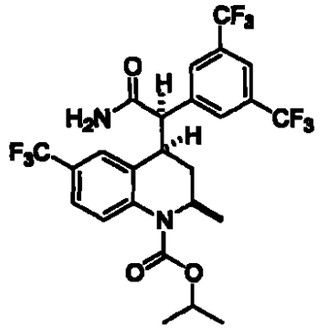


(*S, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

LCMS (ESI+): 571 (MH+)

^{1}H-NMR ($CDCl_3$): δ 0.87 (m, 1H), 1.08 (d, 3H), 1.26 (d, 3H), 1.32 (d, 3H), 1.68 (m, 1H), 3.44 (t, 1H), 3.84 (d, 1H), 4.26 (m, 1H), 5.02 (m,1H), 5.69 (bs, 1H), 6.01 (bs, 1H), 7.47 (s, 1H), 7.49 (d, 1H), 7.54 (d, 1H), 7.87 (s, 3H).

Example 497

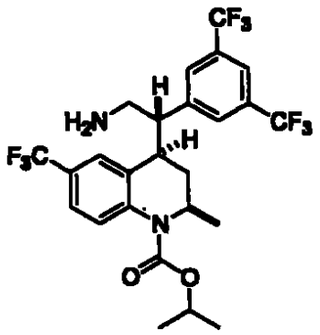


(*RS, RS, RS*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carbamoyl-methyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

LCMS (ESI+): 571 (MH+)

^{1}H-NMR ($CDCl_3$): δ 0.87 (m, 1H), 1.16 (d, 3H), 1.24 (d, 3H), 1.28 (d, 3H), 2.54 (m, 1H), 3.37 (t, 1H), 4.00 (d, 1H), 4.48 (m, 1H), 5.04 (m,1H), 6.02 (bs, 1H), 6.33 (bs, 1H), 7.00 (s, 1H), 7.36 (d, 1H), 7.55 (d, 1H), 7.81 (s, 1H), 7.98 (s, 2H).

Example 498

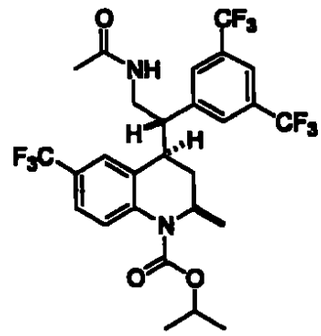


(*RS, RS, SR*)-4-[2-Amino-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

LCMS (ESI+): 557 (MH+)

^{1}H-NMR ($CDCl_3$): δ 0.80 (m, 1H), 1.04 (d, 3H), 1.28 (d, 3H), 1.34 (d, 3H), 1.76 (m, 1H), 2.75 (t, 1H), 3.11 (m, 1H), 3.35 (m, 1H), 3.46 (m,1H), 4.26 (m, 1H), 5.08 (m, 1H), 7.54 (m, 3H), 7.77 (s, 2H), 7.84 (s, 1H).

Example 499

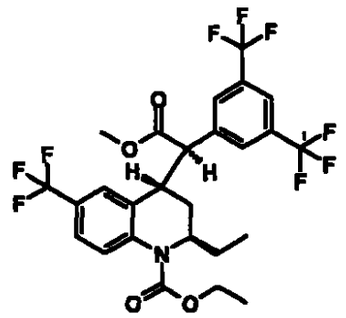


(*RS, RS, SR*)-4-[2-Acetylamino-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

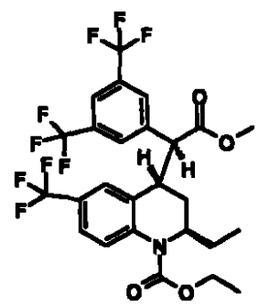
LCMS (ESI+): 599 (MH+)

^{1}H-NMR ($CDCl_3$): δ 0.78 (m, 1H), 1.04 (d, 3H), 1.28 (d, 3H), 1.34 (d, 3H), 1.76 (m, 1H), 1.93 (s, 3H), 2.68 (s, 1H), 3.01 (m, 1H), 3.72 (m, 1H), 4.26 (m, 1H), 4.37 (m, 1H), 5.08 (m, 1H), 5.40 (m, 1H), 7.53 (s, 2H), 7.70 (s, 2H), 7.85 (s, 1H), 8.41 (s, 1H).

Examples 500 and 501



(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R, S, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of 3,5-bis(trifluoromethylphenyl)acetic acid methyl ester (1.41g, 4.93mmol) in anhydrous N,N-dimethylformamide (3mL) was added sodium hydride (60% mineral oil dispersion, 6.55mmol, 262mg) and the mixture was stirred at room temperature for 60min. A solution of (*R*)-4-chloro-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (1.10g, 3.28mmol, mixture of isomers, Preparation 14) in anhydrous N,N-dimethylformamide (1.5mL) was added and the mixture was stirred at room temperature for 72hr. Water (20mL) was added and the mixture was extracted with diethyl ether (3 x 50mL) and the organic extract was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give the crude product as a yellow oil (~2g). Purification was achieved using radial chromatography (Chromatron model 7924T, Harrison Research, Palo Alto, CA) with a 4mm silica gel rotor eluting with hexanes/ethyl acetate 9:1 to give the title compounds:

(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (first eluting diastereoisomer)

MS: 586.0 $[M+H]^+$ found

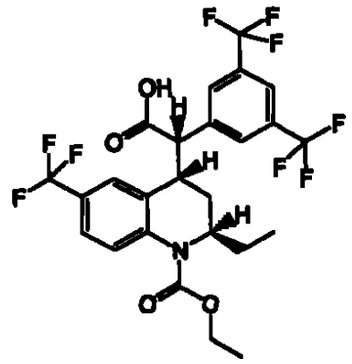
^{1}H-NMR ($CDCl_3$) δ 7.90 (s, 2H), 7.67 (s, 1H), 7.59 (d, J=8.30Hz, 1H), 7.62 (d, J=8.30Hz, 1H), 7.61 (s, 1H), 4.39-4.27 (m, 2H), 4.27-4.18 (m, 1H), 3.78 (d, J=11.61Hz, 1H), 3.59 (m, 1H), 3.48 (s, 3H), 1.76 (ddd, J=14.10, 8.30, 3.30Hz, 1H), 1.61-1.55 (m, 1H),1.57-1.50 (m, 1H), 1.48-1.40 (m, 1H), 1.35 (t, J=7.47Hz, 3H), 0.73 (t, J=7.47Hz, 3H).

(*R, S, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (536mg, second eluting diastereoisomer)

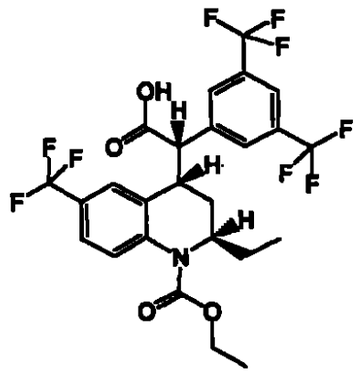
MS: 586.0 $[M+H]^+$ found

^{1}H-NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.42 (d, J=8.30Hz, 1H), 7.40 (s, 2H), 7.33 (dd, J=8.30, 1.66Hz, 1H), 6.47 (d, J=1.66Hz, 1H), 4.55-4.47 (m, 1H), 4.34 (m, 1H), 4.32 (m,1H), 3.63 (d, J=11.61Hz, 1H), 3.60 (s, 3H), 3.43 (ddd, J=11.61, 4.98, 2.49Hz, 1H), 2.44 (ddd, J=14.11, 8.30, 2.49Hz, 1H), 1.81 (ddd, J=14.10, 8.30, 4.98Hz, 1H), 1.67 (m, 1H),1.51 (m, 1H), 1.33 (t, J=7.47Hz, 3H), 0.85 (t, J=7.47Hz, 3H).

Examples 502 and 503



(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *S*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A mixture of (*R*, *S*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Example 501, 100mg, 0.171mmol), aqueous sodium hydroxide (2N, 0.512mL, 1.024mmol) and anhydrous tetrahydrofuran (2mL) was stirred at room temperature for 2 days before adding 2N hydrochloric acid (1.5mL). The mixture was diluted with acetonitrile and evaporated to dryness under vacuum to give the crude product as an oil (128mg). Purification was achieved using radial chromatography (Chromatron model 7924T, Harrison Research, Palo Alto, CA) with a 4mm silica gel rotor eluting with hexanes/ethyl acetate 55:45 to give the title compounds:

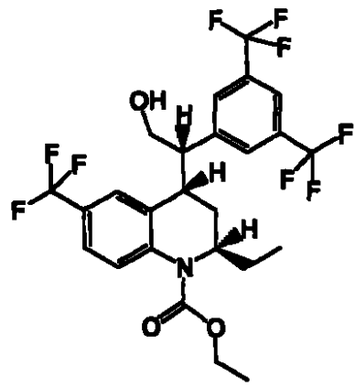
First eluting: (*R*, *S*, *R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (14mg);

^{1}H-NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.88 (s, 2H), 7.55 (m, 1H), 7.51 (m, 1H), 7.49 (m, 1H), 4.32 (m, 1H), 4.27 (m, 1H), 4.21 (m, 1H), 3.80 (d, J=10.79Hz, 1H), 3.57 (m, 1H), 1.78 (m, 1H), 1.55 (m, 2H), 1.43 (m, 1H), 1.32 (t, J=7.47Hz, 3H), 0.71 (t, J=7.47Hz, 3H).

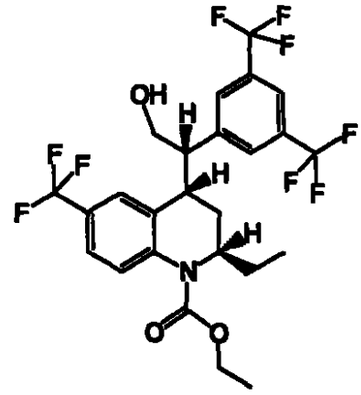
Second eluting: (*R*, *S*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (32mg)

^{1}H-NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.45 (s, 2H), 7.41 (m, 1H), 7.34 (m, 1H), 6.51 (brs, 1H), 4.55 (m, 1H), 4.32 (m, 2H), 3.85 (d, J=10.79Hz, 1H), 3.43 (m, 1H), 2.55 (m, 1H), 1.81 (m, 1H), 1.63 (m, 1H), 1.60 (m, 1H), 1.31 (t, J=7.47Hz, 3H), 0.84 (t, J=7.47Hz, 3H).

Examples 504 and 505



(*R*, *S*, *R*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester



(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

To a solution of (*R*, *S*, *R*)- and (*R*, *S*, *S*)- 4-[(3,5-bis-trifluoromethyl-phenyl)-carboxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Examples 502 and 503 as prepared above but isomers not separated, 143mg, 0.25mmol) in tetrahydrofuran (3mL) under nitrogen was added borane-dimethylsulfide complex (2M in tetrahydrofuran, 0.25mL, 0.5mmol). After 24hr the mixture was diluted with methanol (1mL) and evaporated to dryness under vacuum. To the residue was added 2N hydrochloric acid (3mL), the mixture was stirred for 10min and then extracted with diethyl ether (3 x 15mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum to give the crude product as an oil (175mg). Purification was achieved using radial chromatography (Chromatron model 7924T, Harrison Research, Palo Alto, CA) with

a 1mm silica gel rotor eluting with a hexanes/ethyl acetate gradient from 4:1 to 7:3 to give the title compounds:

First eluting: (*R*, *S*, *R*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (9mg)

MS: 558.3 $[M+H]^+$ found.

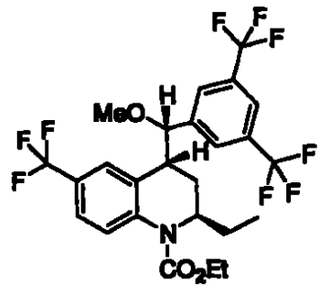
^{1}H-NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.79 (s, 2H), 7.60 (m, 1H), 7.53 (brs, 1H), 7.52 (m, 1H), 4.35 (m, 1H), 4.24 (m, 1H), 4.16 (m, 1H), 3.71 (m, 2H), 3.34 (m, 1H), 2.99 (m, 1H), 1.78 (m, 1H), 1.57 (m, 2H), 1.57 (m, 1H), 1.45 (m, 1H), 1.33 (t, J=7.47Hz, 3H), 0.71 (t, J=7.47Hz, 3H).

Second eluting: (*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (30mg)

MS: 558.5 $[M+H]^+$ found.

^{1}H-NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.40 (m, 1H), 7.39 (s, 2H), 7.32 (m, 1H), 6.62 (brs, 1H) 4.48 (m, 1H), 4.25 (m, 2H), 4.15 (m, 2H), 3.13 (m, 2H), 2.60 (m, 1H), 1.69 (m, 3H), 1.50 (m, 1H), 1.29 (t, J=7.47Hz, 3H), 0.86 (t, J=7.47Hz, 3H).

Example 506



(*R*, *R*, *S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

[(*R*, *R*, *S*)]- 4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (0.030 grams, 0.055 mmol, 1 eq) was placed in a round bottomed flask equipped with a magnetic stir bar. DMSO (1.0 mL) was added followed by the addition of (0.012grams0.221 mmol, 4 eq) potassium hydroxide and (0.016 grams, 0.110 mmol, 2 eq) methyl iodide at room temperature. After 1.5 hour, the reaction mixture was quenched with 1N

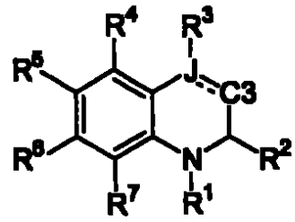
HCl, extracted 3 times with ethyl acetate and dried over sodium sulfate. The crude material was purified on silica gel chromatography to provide the title compound.
LCMS (ESI+): 551 (MH+).
^{1}H NMR ($CDCl_3$): δ7 0.95 (t, 3H), 1.31 (t, 3H), 1.41 (m, 1H), 1.60 (m, 1H), 2.6 (m, 1H), 2.90 (m, 1H), 3.20 (s, 3H), 4.33 (m, 2H), 4.45 (m, 1H), 6.60 (s, 1H), 7.2- (s, 2H), 7.30 (d, 1H).7.5 (d, 1H) 7.70 (s, 1H).

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application for all purposes.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound according to Formula I



Formula I

Wherein

C3 is carbon;

J is nitrogen or carbon, wherein if J is carbon, then the bond between C3 and J is a single or double bond and if J is nitrogen, then the bond between C3 and J is a single bond;

R^1 is Y, W-X or W-Y^1; wherein W is a carbonyl, thiocarbonyl, sulfinyl or sulfonyl; X is -O-Y, -S-Y, -N(H)-Y or -N-$(Y)_2$; Y for each occurrence is independently Z or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z; and Y^1 for each occurrence is independently Z or a fully saturated, partially unsaturated or fully unsaturated one to ten membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen, sulfur and nitrogen and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-, or di-substituted with oxo, and said carbon chain is optionally mono-substituted with Z; wherein Z is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or

a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C_2-C_8)alkenyl, (C_1-C_8) alkyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino, said (C_1-C_8)alkyl or (C_1-C_8)alkoxy substituent is also optionally substituted with from one to nine fluorines;

R^2 is a partially saturated, fully saturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than the connecting carbon, may optionally be replaced with one or two heteroatoms selected independently from oxygen and sulfur, and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo, said carbon is optionally mono-substituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to seven membered ring optionally having one to two heteroatoms selected independently from oxygen and sulfur, wherein said R^2 ring is optionally attached through (C_1-C_4)alkyl; wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, (C_2-C_8)alkenyl, (C_1-C_8) alkyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, oxo or (C_1-C_8)alkyloxycarbonyl;

R^3 is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain having C4a, wherein C4a is a carbon atom that connects to J, wherein each carbon in the carbon chain may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen, and said carbon is optionally mono-, di- or tri-substituted with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is

mono, di-, or tri-substituted with V at C4a or the R^3 carbon adjacent to C4a; provided that in R^3, when J is carbon, it is other than C4a that is optionally replaced with one heteroatom; and provided that in R^3, when J is nitrogen, it is other than C4a that is optionally replaced with a heteroatom and it is other than C4a that is optionally mono-substituted with hydroxy or nitrogen; wherein V is a partially saturated, fully saturated or fully unsaturated three to eight membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen such that V is not imidazolyl or a fully saturated heterocyclic nitrogen-containing ring wherein nitrogen of the ring is connected to the R^3 group; a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; or a tricyclic ring consisting of three fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with V^1, (C_1-C_6)alkyl-V^1, C(O)-V^1, O-(C_0-C_6)alkyl-V^1, (C_1-C_6)alkyl-O-V^1, C(O)-mono-N- or di-N,N-(C_1-C_6)alkyl-V^1, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl, (C_1-C_4)alkylsulfonyl, mono-N- or di-N,N-(C_1-C_6)alkylsulfonyl, amino, nitro, cyano, oxo, carboxamoyl, mono-N- or di-N,N-(C_1-C_6) alkylcarboxamoyl, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, wherein said (C_1-C_6)alkyl or (C_2-C_6)alkenyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, wherein each (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfonyl or (C_2-C_6)alkenyl substituents are also optionally substituted with from one to nine fluorines; wherein V^1 is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said V^1 substituent is optionally mono-, di-, tri-, tetra- or penta-substituted independently with halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, oxo, amino, nitro, cyano, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-

N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-substituted with oxo, said (C_1-C_8)alkyl or (C_1-C_8)alkoxy substituent is also optionally substituted with from one to nine fluorines; and

each of R^4, R^5, R^6 and R^7 are independently hydrogen, a bond, nitro or halo wherein said bond is substituted with T or a partially saturated, fully saturated or fully unsaturated (C_1-C_{12}) straight or branched carbon chain wherein each carbon may optionally be replaced with one or two heteroatoms per carbon chain wherein the heteroatoms are selected independently from oxygen, sulfur and nitrogen, wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is optionally mono-substituted with T; wherein T is a partially saturated, fully saturated or fully unsaturated three to twelve membered ring optionally having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen; and said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-, di- or tri-substituted independently with hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino, said (C_1-C_8)alkyl or (C_1-C_8)alkoxy substituent also optionally has from one to nine fluorines;

R^4 and R^5, R^5 and R^6, and/or R^6 and R^7 may optionally be taken together and can form at least one ring that is a partially saturated or fully unsaturated four to eight membered ring optionally having one to three heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein each ring formed by R^4 and R^5, or R^5 and R^6, and/or R^6 and R^7 is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_8)alkyl, (C_1-C_4)alkylsulfonyl, (C_2-C_8)alkenyl, hydroxy, (C_1-C_8)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_8)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_8)alkylamino wherein said (C_1-C_8)alkyl substituent is optionally mono-,

di- or tri-substituted independently with hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, nitro, cyano, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino, said (C_1-C_6)alkyl substituent also optionally has from one to nine fluorines;

or a pharmaceutically acceptable salt or prodrug thereof;

with the following provisos:

a) when there is a single bond between C3 and J, and R^3 is a fully saturated one to six membered straight or branched carbon chain substituted on C4a with V then R^1 is other than C(O)-(C_1-C_4)alkyl optionally mono-, di- or tri-substituted with halo and R^1 is other than C(O)-monocyclicaromatic ring; or

b) when there is a single bond between C3 and J, and R^3 is –C(O)-O-V, and R^2 is phenyl then R^1 is other than (C_1-C_4)alkyl; and

c) when there is a double bond between C3 and J, and R^2 is methyl then R^3 is other than -CH_2-O-V, –CH_2-V or –CH_2-CH_2-V.

2. A compound of claim 1 wherein

J is carbon;

R^1 is W-X;

W is carbonyl;

X is -O-Y;

Y for each occurrence is independently (C_1-C_6)alkyl, said (C_1-C_6)alkyl optionally having one to nine fluorines or said (C_1-C_6)alkyl optionally mono-substituted with Z;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, nitro, cyano, oxo, or (C_1-C_4)alkyloxycarbonyl, said (C_1-C_4)alkyl or (C_1-C_4)alkoxy is optionally substituted with from one to nine fluorines;

R^2 is beta and is a partially saturated, fully saturated or fully unsaturated (C_1-C_6) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo or hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully

unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygen and sulfur;

wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_6)alkoxy, amino, nitro, (C_1-C_4)alkyloxycarbonyl or carboxy;

wherein R^3 is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than C4a, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen, and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with cyano, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono- or di-substituted with hydrogen or oxo, and said carbon chain is optionally mono, di-, or tri-substituted with V at C4a or at the R^3 carbon adjacent to C4a; V is a three, four, five or six membered partially saturated, fully saturated or fully unsaturated ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen such that V is not imidazolyl or a fully saturated heterocyclic nitrogen-containing ring wherein nitrogen of the ring is connected to the R^3 group;

wherein said V ring is optionally mono-, di-, tri-, tetra- or penta-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, nitro, cyano or oxo, wherein said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines;

R^4 is hydrogen;

R^5 and R^6 are each independently hydrogen, halo, T, (C_1-C_6)alkoxy or (C_1-C_6)alkyl, said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally having from one to nine fluorines or said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein

said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines;

R^7 is hydrogen;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2 wherein

Y is methyl, ethyl, 1-propyl, 2-propyl or tert-butyl;

R^2 is methyl, ethyl, 2-propyl, cyclopropyl or cyclobutyl;

R^3 is -C(O)-V, -C(OH)(C(O)OCH_3)(V), -CH(F)(V), -CF_2(V), -CH(OCH_3)(V), -CH(C(O)OCH_3)(V), -CH(CN)(V), -CH(OH)(V), -CH_2(V), -CH(NH_2)(V), -CH(NH(CH_3))(V), -CH(C(O)NH_2)(V), -CH(CH_2OH)V, -CH(CH_2OCH_3)V, -CH($CH_2OC(O)CH_3$)V, -CH(CH_2F)V, or -CH(CH_2NH_2)V; and

V is phenyl optionally mono-, di- or tri-substituted independently with halo, nitro, or (C_1-C_2)alkyl, wherein said (C_1-C_2)alkyl optionally has from one to five fluorines;

R^5 and R^6 are each independently hydrogen, methyl, methoxy or chloro; said methoxy optionally having from one to three fluorines, said methyl optionally having from one to three fluorines;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 3 wherein

Y is ethyl;

R^2 is ethyl or methyl;

R^3 is (3,5-bis-(trifluoromethyl)-phenyl)-hydroxy-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl; (3,5-bis-trifluoromethyl-phenyl)-cyano-methyl, 3,5-bis-trifluoromethyl-benzoyl; (3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl; (3,5-bis-trifluoromethyl-phenyl)-fluoro-methyl; (3,5-bis-trifluoromethyl-phenyl)-difluoro-methyl; (3,5-bis-(trifluoromethyl)-benzyl); (3,5-bis-trifluoromethyl-phenylcarbamoyl)-methyl; amino-(3,5-bis-(trifluoromethyl)-phenyl)-methyl; (3,5-bis-(trifluoromethyl)-phenyl)-methylamine-methyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-amino-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-fluoro-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-methoxy-ethyl; 1-(3,5-bis-(trifluoromethyl)-phenyl)-2-hydroxy-ethyl; or 2-acetoxy-1-(3,5-bis-(trifluoromethyl)-phenyl)-ethyl;

R^5 is methoxy or trifluoromethyl; and

R^6 is hydrogen or methoxy;

or a pharmaceutically acceptable salt thereof.

5. A compound of claim 1 wherein

J is nitrogen;

the bond between C3 and J is a single bond;

R^1 is W-X;

W is carbonyl;

X is –O-Y;

Y for each occurrence is independently (C_1-C_8)alkyl, said (C_1-C_8)alkyl optionally having one to nine fluorines or said (C_1-C_8)alkyl optionally mono-substituted with Z;

wherein Z is a partially saturated, fully saturated or fully unsaturated three to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said Z substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, nitro, cyano, oxo, or (C_1-C_4)alkyloxycarbonyl, said (C_1-C_4)alkyl or (C_1-C_4)alkoxy optionally substituted with from one to nine fluorines;

R^2 is a partially saturated, fully saturated or fully unsaturated (C_1-C_4) straight or branched carbon chain wherein one carbon, other than the connecting carbon, may optionally be replaced with oxygen or sulfur and wherein said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon chain is optionally mono-substituted with oxo, said carbon is optionally monosubstituted with hydroxy, said sulfur is optionally mono- or di-substituted with oxo,; or said R^2 is a partially saturated, fully saturated or fully unsaturated three to five membered ring optionally having one heteroatom selected independently from oxygenand sulfur; wherein said R^2 ring is optionally mono-, di- or tri-substituted independently with halo, hydroxy, (C_1-C_8)alkoxy, amino, nitro, (C_1-C_4)alkyloxycarbonyl or carboxy;

wherein R^3 is a fully saturated, partially unsaturated or fully unsaturated one to six membered straight or branched carbon chain wherein each carbon, other than C4a or the R^3 carbon adjacent to C4a, may optionally be replaced with one heteroatom selected from oxygen, sulfur and nitrogen, and said carbon is optionally mono-, di- or tri-substituted independently with halo, said carbon, other than C4a, is optionally mono-substituted with hydroxy, said carbon is optionally mono-substituted with cyano, said carbon is optionally mono-substituted with oxo or nitrogen, said sulfur is optionally mono- or di-substituted with oxo, said nitrogen is optionally mono-

or di-substituted with hydrogen or oxo, and said carbon chain is optionally mono, di-, or tri-substituted with V at C4a or at the the R^3 carbon adjacent to C4a;

V is a five or six membered partially saturated, fully saturated or fully unsaturated ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen such that V is not imidazolyl or a fully saturated heterocyclic nitrogen-containing ring wherein nitrogen of the ring is connected to the R^3 group; wherein said V ring is optionally mono-, di-, tri-, tetra- or penta-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, nitro, cyano or oxo, wherein said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines;

R^4 is hydrogen;

R^5 and R^6 are each independently hydrogen, halo, T, (C_1-C_6)alkoxy or (C_1-C_6)alkyl, said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally having from one to nine fluorines or said (C_1-C_6)alkoxy or (C_1-C_6)alkyl substituent optionally mono-substituted with T;

wherein T is a partially saturated, fully saturated or fully unsaturated five to six membered ring optionally having one to two heteroatoms selected independently from oxygen, sulfur and nitrogen;

wherein said T substituent is optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, (C_1-C_4)alkylthio, amino, oxo, carboxy, (C_1-C_6)alkyloxycarbonyl, mono-N- or di-N,N-(C_1-C_6)alkylamino wherein said (C_1-C_6)alkyl or (C_1-C_6)alkoxy substituent optionally has from one to nine fluorines;

R^7 is hydrogen;

or a pharmaceutically acceptable salt thereof.

6. A compound of claim 5 wherein

Y is (C_1-C_4)alkyl, wherein said (C_1-C_4)alkyl substituent optionally has one to nine fluorines;

R^2 is (C_1-C_4)alkyl, cyclopropyl or cyclobutyl;

R^3 is -C(O)-V, -CH(C(O)O(C_1-C_3)alkyl)(V), or -CH(CN)(V);

V is phenyl optionally mono-, di- or tri-substituted independently with halo, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, nitro, cyano or oxo wherein said (C_1-C_6)alkyl substituent optionally has from one to nine fluorines;

R^5 and R^6 are each independently hydrogen, (C_1-C_3)alkoxy or (C_1-C_3)alkyl, said (C_1-C_3)alkoxy optionally having from one to nine fluorines, said (C_1-C_3)alkyl optionally having from one to seven fluorines;

or a pharmaceutically acceptable salt thereof.

7. A compound of claim 6 wherein

Y is methyl, ethyl, 1-propyl, 2-propyl or tert-butyl;

R^2 is methyl, ethyl, 2-propyl, cyclopropyl or cyclobutyl;

R^3 is 3,5-bis-trifluoromethyl-benzoyl, (3,5-bis-trifluoromethyl-phenyl)-cyano-methyl, or (3,5-bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl;

R^5 is methyl or trifluoromethyl;

R^6 is hydrogen or methyl.

8. A compound according to claim 1, selected from the group consisting of:

(*R*, *R*, *S*)-4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[Amino-(3,5-bis-trifluoromethyl-phenyl)- methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*)-4-(3,5-bis-trifluoromethyl-benzyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methylaminomethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-methylaminomethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-6,7-dimethoxy-2-methyl-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-6,7-dimethoxy-2-methyl-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *R*)- 4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl- methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, R, R*)-4-[(3,5-bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]- 6,7-dimethoxy-2-methyl- 3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R, S, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxyl-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S, S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-hydroxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, R, S*)-4-[2-Acetoxy-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R, S, S*)-4-[2-Acetoxy-1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-methoxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-methoxy-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-fluoro-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-fluoro-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *R*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-amino-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*, *S*, *S*)-4-[1-(3,5-Bis-trifluoromethyl-phenyl)-2-amino-ethyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*S*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*R*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*S*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*S*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*R*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*R*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6-trifluoromethyl-2H-quinoline-1-carboxylic acid ethyl ester;

(*R*,*S*)-4-(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-benzoyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-fluoro-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R*)-4-(3,5-bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S*)-4-(3,5-bis-trifluoromethyl-benzoyl)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-6,7-dimethoxy-2-methyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,S,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R,R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-hydroxy-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester;

(*R*)-4-(3,5-Bis-trifluoromethyl-benzoyl)-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-cyano-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid methyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester;

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6,7-dimethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester;

(*R,R*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester; and

(*R,S*)-4-[(3,5-Bis-trifluoromethyl-phenyl)-methoxycarbonyl-methyl]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoxaline-1-carboxylic acid ethyl ester;

or a pharmaceutically acceptable salt or prodrug thereof.

9. A method for treating atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction in a mammal by administering to a mammal in need of such treatment an atherosclerosis, coronary artery disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia or myocardial infarction treating amount of a compound of any of claims 1 to 8, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug.

10. A pharmaceutical composition which comprises a therapeutically effective amount of a compound of any of claims 1 to 8, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable vehicle, diluent or carrier.

11. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a compound of any of claims 1 to 8, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug;

a second compound, said second compound being an HMG CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a PPAR modulator, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant; and

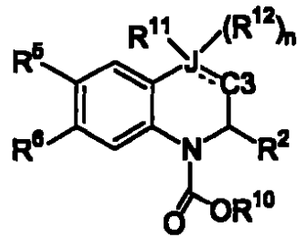
a pharmaceutical vehicle, diluent or carrier.

12. A pharmaceutical combination composition as recited in claim 11 wherein the second compound is an HMG-CoA reductase inhibitor or a PPAR modulator.

13. A pharmaceutical combination composition as recited in claim 12 wherein the second compound is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, rosuvastatin or pitavastatin.

14. A kit for achieving a therapeutic effect in a mammal comprising packaged in association a first therapeutic agent comprising a therapeutically effective amount of a compound of any of claims 1 to 8, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug and a pharmaceutically acceptable carrier, a second therapeutic agent comprising a therapeutically effective amount of an HMG CoA reductase inhibitor, a PPAR modulator, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, slow-release niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant and a pharmaceutically acceptable carrier and directions for administration of said first and second agents to achieve the therapeutic effect.

15. A compound of Formula III



Formula III

wherein

C3 is carbon;

J is carbon, wherein the bond between C3 and J is a single or double bond;

n is zero if the bond between C3 and J is a double bond or one if the bond between C3 and J is a single bond;

R^2 is (C_1-C_4)alkyl, cyclopropyl or cyclobutyl;

R^5 is CF_3;

R^9 is hydrogen;

R^{10} is a fully saturated (C_1-C_4) straight or branched carbon chain;

R^{11} is halo, hydroxy, –C(O)(O(C_1-C_4)alkyl), –C(O)C(O)(O(C_1-C_4)alkyl), –C(O)NH(O(C_1-C_4)alkyl), or –C(O)N((C_1-C_4)alkyl)(O(C_1-C_4)alkyl);

R^{12} is hydrogen or halo, wherein R^{11} is not halo when R^{12} is halo;

or R^{11} and R^{12} are taken together to form =O or N_2;

or a pharmaceutically acceptable salt or prodrug thereof.

COMPUESTOS DE QUINOLINA Y QUINOXALINA

ANTECEDENTES DE LA INVENCIÓN

La invención se refiere a compuestos de quinolina y quinoxalina, a composiciones farmacéuticas que contienen tales inhibidores y al uso de tales inhibidores para aumentar ciertos niveles de lípidos en el plasma, incluyendo la lipoproteína de alta densidad (HDL) del colesterol y para reducir otros niveles de lípidos en plasma, tales como la lipoproteína de baja densidad (LDL) del colesterol y, por consiguiente, para tratar enfermedades que se ven afectadas por los niveles bajos de colesterol HDL y/o niveles altos de colesterol-LDL y triglicéridos, tales como aterosclerosis y enfermedades cardiovasculares en ciertos mamíferos (es decir, los que tienen CETP en su plasma), incluyendo seres humanos.

La aterosclerosis y su enfermedad asociada de la arteria coronaria (CAD) es la principal causa de mortalidad en el mundo industrializado. A pesar de los intentos por modificar los factores de riesgo secundarios (fumar, obesidad, falta de ejercicio) y el tratamiento de la dislipidemia con modificación dietética y terapia con fármacos, la enfermedad cardíaca coronaria (CHD) sigue siendo la causa más común de muerte en los Estados Unidos, donde las enfermedades cardiovasculares representan el 44% de todas las muertes, 53% de las cuales se asocian con la enfermedad cardíaca coronaria aterosclerótica.

Se ha demostrado que el riesgo de desarrollo de esta enfermedad está fuertemente correlacionada con ciertos niveles de lípidos en plasma. Aunque C-LDL alto puede ser la forma más reconocida de dislipidemia, no es de ninguna manera el único lípido asociado que contribuye a la CHD. C-HDL bajo también es un factor de riesgo conocido para la CHD (Gordon, D.J., y col.,: "High density Lipoprotein Cholesterol and Cardiovascular Disease", Circulation, (1989), 79: 8-15).

Los niveles altos de colesterol-LDL y de triglicéridos se correlacionan de forma

positiva, aunque los niveles altos de colesterol-HDL se correlacionan de forma negativa con el riesgo de desarrollar enfermedades cardiovasculares. De esta forma, la dislipidemia no es un perfil de riesgo unitario de CHD aunque puede estar compuesta por una o más alteraciones en los lípidos.

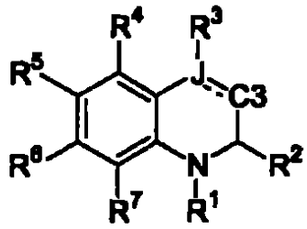
Entre los muchos factores que controlan los niveles en plasma de estos principios dependientes de la enfermedad, la actividad de la proteína de transferencia del éster de colesterol (CETP) afecta a los tres. El papel de esta glicoproteína en plasma de 70.000 daltons que se encuentra en varias especies animales, incluyendo seres humanos, es transferir ésteres de colesterol y triglicéridos entre partículas lipoproteicas, incluyendo lipoproteínas de alta densidad (HDL), lipoproteínas de baja densidad (LDL), lipoproteínas de muy baja densidad (VLDL) y quilomicrones. El resultado neto de la actividad CETP es una disminución del colesterol HDL y un aumento del colesterol LDL. Se cree que este efecto en el perfil lipoproteico es pro-aterogénico, especialmente en sujetos cuyo perfil lipídico constituye un mayor riesgo de CHD.

Hoy día en el mercado no hay terapias que aumenten HDL de forma totalmente satisfactoria. La niacina puede aumentar significativamente la HDL pero tiene serios problemas de tolerancia que reducen la aceptación. Los fibratos y los inhibidores de la HMG CoA reductasa aumentan el C-HDL, pero en algunos pacientes, el resultado es un aumento de proporciones moderadas (~10-12%). Como resultado, existe una necesidad médica no satisfecha de un agente terapéutico aprobado que aumente los niveles de HDL en plasma, por lo tanto, invirtiendo o haciendo más lenta la progresión de la aterosclerosis.

De esta forma, aunque existen diversas terapias anti-aterosclerosis, en este campo de la técnica existe una necesidad y búsqueda continua de terapias alternativas.

SUMARIO DE LA INVENCIÓN

Esta invención se refiere a compuestos de acuerdo con la Fórmula I



Fórmula I

en la que

C3 es carbono;

J es nitrógeno o carbono, donde si J es carbono, entonces el enlace entre C3 y J es un enlace sencillo o doble y si J es nitrógeno, entonces el enlace entre C3 y J es un enlace sencillo;

R^1 es Y, W-X o W-Y^1; donde W es un carbonilo, tiocarbonilo, sulfinilo o sulfonilo; X es -O-Y, -S-Y, -N(H)-Y o -N-$(Y)_2$; Y para cada caso es independientemente Z o una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a diez miembros, lineal o ramificada, donde cada carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con uno o dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con oxo, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con oxo y estando dicha cadena carbonada opcionalmente mono-sustituida con Z; e Y^1 para cada caso es independientemente Z o una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de una a diez miembros, lineal o ramificada, donde cada carbono distinto del carbono de unión, puede reemplazarse

opcionalmente con uno o dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente sustituido con oxo, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con oxo y estando dicha cadena carbonada opcionalmente mono-sustituida con Z; donde Z es un anillo de tres a ocho miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente Z está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquenilo (C_2-C_6), alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) estando dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) opcionalmente sustituido con uno a nueve átomos de flúor;

R^2 es una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, donde cada carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con uno o dos heteroátomos seleccionados independientemente entre oxígeno y azufre y donde dicho

carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicha cadena carbonada opcionalmente mono-sustituida con oxo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho azufre opcionalmente mono- o di-sustituido con oxo; o dicho R^2 es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a siete miembros que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno y azufre, donde dicho anillo R^2 está opcionalmente unido mediante un alquilo (C_1-C_4); donde dicho anillo R^2 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquenilo (C_2-C_6), alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), oxo o alquiloxicarbonilo (C_1-C_6);

R^3 es una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, que contiene C4a, donde C4a es un átomo de carbono que conecta con J, donde cada carbono de la cadena carbonada puede reemplazarse opcionalmente con un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con oxo o nitrógeno, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo, y estando dicha cadena carbonada mono, di- o tri-sustituida con V en C4a en el carbono R^3 adyacente a C4a; siempre que en R^3, cuando J es carbono, sea distinto de C4a que está opcionalmente reemplazado con un heteroátomo; y siempre que en R^3, cuando J es nitrógeno, sea distinto

de C4a que está opcionalmente reemplazado con un heteroátomo y sea distinto de C4a que está opcionalmente mono-sustituido con hidroxi o nitrógeno; donde V es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a ocho miembros que tiene opcionalmente de uno o cuatro heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno tal que V no es imidazolilo o un anillo heterocíclico totalmente saturado que contiene nitrógeno donde el nitrógeno del anillo está unido al grupo R^3; un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; o un anillo tricíclico que consiste en tres anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente V está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con V^1, alquil (C_1-C_6)-V^1, C(O)-V^1, C-(O)-V^1, O-alquil (C_0-C_6)-V^1, alquilo (C_1-C_6)-O-V^1, C(O)-mono-N- o di-N,N-alquil (C_1-C_6)-V^1, halo, alquilo (C_1-C_6), alquenilo (C_2-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), alquilsulfinilo (C_1-C_4), alquilsulfonilo (C_1-C_4), mono-N- o di-N,N-alquilsulfonilo (C_1-C_6), amino, nitro, ciano, oxo, carboxamoílo, mono-N- o di-N,N-alquilcarboxamoílo (C_1-C_6), carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6), donde dicho sustituyente alquilo (C_1-C_6) o alquenilo (C_2-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6), donde cada uno de los sustituyentes alquilo (C_1-C_6), alcoxi (C_1-C_6), alquiltio (C_1-C_4), alquilsulfonilo (C_1-C_4) o alquenilo (C_2-C_6) también están

opcionalmente sustituidos con uno a nueve átomos de flúor; donde V^1 es un anillo de tres a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente V^1 está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), hidroxi, oxo, amino, nitro, ciano, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-sustituido con oxo, dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) también está opcionalmente sustituido con uno a nueve átomos de flúor; y

cada uno de R^4, R^5, R^6 y R^7 es independientemente hidrógeno, un enlace, nitro o halo donde dicho enlace está sustituido con T o una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada (C_1-C_{12}), lineal o ramificada, donde cada carbono puede reemplazarse opcionalmente con uno o dos heteroátomos por cadena carbonada donde los heteroátomos se seleccionan independientemente entre oxígeno, azufre y nitrógeno, donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente sustituido con oxo o nitrógeno, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo y estando dicha cadena carbonada opcionalmente mono-sustituida con T; donde T es un anillo de tres a doce miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene

opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros condensados parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente T está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), alquenilo (C_2-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) teniendo opcionalmente dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) de uno a nueve átomos de flúor;

R^4 y R^5, R^5 y R^6, y/o R^6 y R^7 se pueden tomar conjuntamente y formar al menos un anillo que es un anillo parcialmente saturado o totalmente insaturado de cuatro a ocho miembros que tiene opcionalmente de uno a tres heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; donde cada uno de los anillo formados por R^4 y R^5 o R^5 y R^6, y/o R^6 y R^7 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), alquilsulfonilo (C_1-C_4), alquenilo (C_2-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) teniendo dicho sustituyente alquilo (C_1-C_6) también opcionalmente de uno a nueve átomos de flúor;

o una sal o profármaco farmacéuticamente aceptable del mismo;

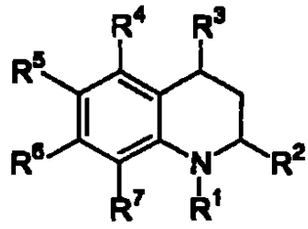
con las siguientes condiciones:

a) cuando hay un enlace sencillo entre C3 y J y R^3 es una cadena carbonada totalmente saturada de uno a seis miembros lineal o ramificada sustituida en C4a con V entonces R^1 es distinto de C(O)-alquilo (C_1-C_4) opcionalmente mono-, di- o tri-sustituido con halo y R^1 es distinto de un anillo C(O)-monociclicaromático; o

b) cuando hay un enlace sencillo entre C3 y J, y R^3 es -C(O)-O-V, y R^2 es fenilo entonces R^1 es distinto de alquilo (C_1-C_4); y

c) cuando hay un enlace doble entre C3 y J, y R^2 es metilo entonces R^3 es distinto de -CH_2-O-V, -CH_2-V o -CH_2-CH_2-V.

Además, la presente invención se refiere a compuestos de acuerdo con la Fórmula II



Fórmula II

en la que

R^1 es W-X;

W es carbonilo;

X es -O-Y;

Y para cada caso es independientemente alquilo (C_1-C_6), teniendo opcionalmente dicho alquilo (C_1-C_6) de uno a nueve átomos de flúor o estando dicho alquilo (C_1-C_6) opcionalmente mono-sustituido con Z;

donde Z es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a seis miembros que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente Z está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), alquiltio (C_1-C_4), nitro, ciano, oxo o alquiloxicarbonilo (C_1-C_4), estando dicho alquilo (C_1-C_4) opcionalmente sustituido con uno a nueve átomos de flúor;

R^2 es una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada (C_1-C_4), lineal o ramificada, donde cada carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con un heteroátomo seleccionado independientemente entre oxígeno y azufre y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicha cadena carbonada opcionalmente mono-sustituida con oxo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho azufre opcionalmente mono- o di-sustituido con oxo; o dicho R^2 es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a cinco miembros que tiene opcionalmente un heteroátomo seleccionado independientemente entre oxígeno y azufre

donde dicho anillo R^2 está opcionalmente mono-, di- o tri-sustituido independientemente con halo o alcoxi (C_1-C_6);

donde R^3 es $-CH_2NR^8R^9$ o $-C(O)NR^8R^9$;

donde R^8 y R^9 son independientemente hidrógeno o una cadena carbonada lineal (C_1-C_2) donde al menos uno de R^8 y R^9 no son hidrógeno y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono, distinto del carbono de unión, opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con oxo y estando dicha cadena

carbonada mono, di- o tri-sustituida con V^3, donde R^8 o R^9 está sustituido con V^3, o R^8 y R^9 están ambos sustituidos con V^3;

donde V^3 es un anillo de tres a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno, o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno;

donde dicho sustituyente V^3 está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con V^4, alquil (C_1-C_6)-V^4, C(O)-V^4, O-alquil (C_0-C_6)-V^4, alquil (C_1-C_6)-O-V^4, halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), hidroxi, oxo, amino, nitro, ciano, alquiltio (C_1-C_4), alquilsulfinilo (C_1-C_4), alquilsulfonilo (C_1-C_4), mono-N- o di-N,N-alquilsulfonilo (C_1-C_6), alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6), donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-sustituido con oxo, estando dicho sustituyente alquilo (C_1-C_6) opcionalmente monosustituido con hidroxi, estando también dichos sustituyentes alquilo (C_1-C_6) o alcoxi (C_1-C_6) opcionalmente sustituidos con uno a nueve átomos de flúor.

donde V^4 es un anillo de tres a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno, o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno;

donde dicho sustituyente V^4 está opcionalmente mono-, di-, tri- o tetra-sustituido independientemente con halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), hidroxi, oxo, amino, nitro, ciano, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-sustituido con oxo, dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) también está opcionalmente sustituido con uno a nueve átomos de flúor;

o donde R^8 y R^9 se toman conjuntamente para formar un anillo de tres a ocho miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros condensados parcialmente saturados, totalmente saturados o totalmente insaturados, seleccionados independientemente entre nitrógeno, azufre y oxígeno;

R^4 es hidrógeno;

cada uno de R^5 y R^6 es independientemente hidrógeno, halo, T, alcoxi (C_1-C_6) o alquilo (C_1-C_6), teniendo dicho sustituyente alcoxi (C_1-C_6) o alquilo (C_1-C_6) opcionalmente de uno a nueve átomos de flúor o estando dicho alcoxi (C_1-C_6) o alquilo (C_1-C_6) opcionalmente mono-sustituido con T;

donde T es un anillo de cinco a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

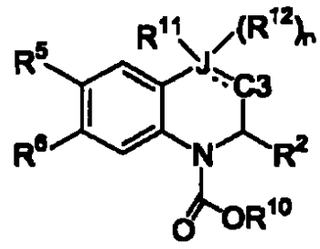
donde dicho sustituyente T está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) tiene opcionalmente de uno a nueve átomos de

flúor;

R^7 es hidrógeno;

o una sal o profármaco farmacéuticamente aceptable del mismo.

Además, la presente invención proporciona compuestos de Fórmula III



Fórmula III

en la que

C3 es carbono;

J es carbono, donde el enlace entre C3 y J es un enlace sencillo o doble;

n es cero si el enlace entre C3 y J es un enlace doble o uno si el enlace entre C3 y J es un enlace sencillo;

R^2 es alquilo (C_1-C_4), ciclopropilo o ciclobutilo;

R^5 es CF_3;

R^6 es hidrógeno;

R^{10} es una cadena carbonada totalmente saturada (C_1-C_4) lineal o ramificada;

R^{11} es halo, hidroxi, -C(O)(O alquilo (C_1-C_4)), -C(O)C(O)(O alquilo (C_1-C_4)), –C(O)NH(O alquilo (C_1-C_4)) o -C(O)N((alquilo (C_1-C_4))(O alquilo (C_1-C_4));

R^{12} es hidrógeno o halo, donde R^{11} no es halo cuando R^{12} es halo;

o R^{11} y R^{12} se toman conjuntamente para formar oxo o N_2;

o una sal o profármaco farmacéuticamente aceptable del mismo.

Además, la presente invención proporciona procedimientos para tratar

aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio en un mamífero administrando a un mamífero en necesidad de tal tratamiento una cantidad para tratar aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio de un compuesto de la presente invención o una forma farmacéuticamente aceptable de dicho compuesto.

Además, la presente invención proporciona composiciones farmacéuticas que comprenden una cantidad terapéuticamente eficaz de un compuesto de la presente invención, o una forma farmacéuticamente aceptable de dicho compuesto y un vehículo, diluyente o excipiente farmacéuticamente aceptable.

Además, la presente invención proporciona composiciones farmacéuticas para el tratamiento de la aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio en un mamífero que comprende una cantidad terapéuticamente eficaz de un compuesto de la presente invención y un vehículo, diluyente o excipiente farmacéuticamente aceptable.

Además, la presente invención proporciona composiciones de combinación farmacéutica que comprenden: una cantidad terapéuticamente eficaz de una composición que comprende

un primer compuesto, siendo dicho primer compuesto un compuesto de la presente invención, o una forma farmacéuticamente aceptable de dicho compuesto;

un segundo compuesto, siendo dicho segundo compuesto un inhibidor de la HMG CoA reductasa, un inhibidor de la secreción de MTP/Apo B, un modulador de PPAR, un inhibidor de la recaptación de ácidos biliares, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, niacina de liberación lenta, una combinación de niacina y lovastatina, una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT o un secuestrador de los ácidos biliares (preferiblemente un inhibidor de la HMG-CoA reductasa, un modulador de PPAR, lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, rosuvastatina o pitavastatina); y

un vehículo, diluyente o excipiente farmacéutico. Esta composición puede usarse para tratar las enfermedades mencionadas anteriormente, incluyendo aterosclerosis.

Además, la presente invención proporciona un kit para conseguir un efecto terapéutico en un mamífero que comprende, envasado conjuntamente con un primer agente terapéutico que comprende una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1, 8, 12 ó 13, un profármaco del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco y un vehículo farmacéuticamente aceptable, un segundo agente terapéutico que comprende una cantidad terapéuticamente eficaz de un inhibidor de la HMG CoA reductasa, un modulador de PPAR, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, niacina de liberación lenta, una combinación de niacina y lovastatina, una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT o un secuestrador de los ácidos biliares y un vehículo farmacéuticamente aceptable e instrucciones para la administración de dicho primer y segundo agente para

conseguir el efecto terapéutico.

Se entenderá que tanto la descripción general anterior como la siguiente descripción detallada sólo son ilustrativas y explicativas y no restringen la invención, como se reivindica.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención se puede entender más fácilmente en referencia a la siguiente descripción detallada de ejemplos de realizaciones de la invención y los ejemplos incluidos en las mismas.

Antes de describir los compuestos, composiciones y procedimientos de la presente invención, debe apreciarse que esta invención no está limitada a los procedimientos específicos sintéticos de fabricación que por supuesto pueden variar. También debe apreciarse que la terminología usada en este documento tiene el propósito de describir exclusivamente realizaciones particulares y no pretende limitar la invención.

La presente invención también se refiere a las sales de adición de ácidos farmacéuticamente aceptables de la presente invención. Los ácidos que se usan para preparar las sales de adición de ácidos de los compuestos básicos mencionados anteriormente son aquellos que forman sales de adición de ácidos no tóxicas, es decir, sales que contienen aniones farmacológicamente aceptables tales como clorhidrato, bromhidrato, yodhidrato, nitrato, sulfato, bisulfato, fosfato, fosfato ácido, acetato, lactato, citrato, citrato ácido, tartrato, bitartrato, succinato, maleato, fumarato, bencenosulfonato, p-toluenosulfonato y pamoato (es decir, sales de 1,1'-metilen-bis-(2-hidroxi-3-naftoato)).

La invención también se refiere a sales de adición de bases de los compuestos de la presente invención. Las bases químicas que se pueden usar como reactivos para

preparar las sales de bases farmacéuticamente aceptables de aquellos compuestos de la presente invención que son de naturaleza ácida son aquellas que forman sales de bases no tóxicas con tales compuestos. Tales sales de bases no tóxicas incluyen, sin limitación, aquellas derivadas de cationes farmacéuticamente aceptables tales como cationes de metales alcalinos (por ejemplo, potasio y sodio) y cationes de metales alcalinotérreos (por ejemplo, calcio y magnesio), sales de amonio o sales de adición de amina solubles en agua tales como N-metilglucamina-(meglumina) y el alcanolamonio inferior y otras sales de bases de aminas orgánicas farmacéuticamente aceptables.

El químico de experiencia habitual reconocerá que ciertos compuestos de esta invención contendrán uno o más átomos que pueden estar en una configuración estereoquímica o geométrica particular, dando lugar a esteroisómeros e isómeros configuracionales. Todos estos isómeros y mezclas de los mismos están incluidos en esta invención. Los hidratos y solvatos de los compuestos de esta invención también están incluidos.

Cuando los compuestos de la presente invención tienen dos o más centros estereogénicos y la estereoquímica absoluta o relativa se da en el nombre, las designaciones R y S se refieren respectivamente a cada centro estereogénico en orden numérico ascendente (1, 2, 3 etc.) de acuerdo con los procedimientos de numeración convencionales de IUPAC para cada molécula. Cuando los compuestos de la presente invención tienen uno o más centros estereogénicos y no se da la estereoquímica en el nombre o estructura, debe apreciarse que el nombre o estructura pretende abarcar todas las formas del compuesto, incluyendo la forma racémica.

Los compuestos de la presente invención pueden contener enlaces dobles olefínicos. Cuando tales enlaces están presentes, los compuestos de la invención existen en configuraciones cis y trans y como mezclas de las mismas. El término "cis" se refiere

a la orientación de dos sustituyentes con referencia al otro y al plano del anillo (ambos "arriba"o ambos "abajo"). De forma análoga, el término "trans" se refiere a la orientación de dos sustituyentes con referencia al otro y al plano del anillo (estando los sustituyentes en lados opuestos del anillo).

Alfa y Beta hacen referencia a la orientación de un sustituyente con referencia al plano del anillo. Beta es por encima del plano y Alfa es por debajo del plano del anillo.

Esta invención también incluye compuestos marcados con isótopos, que son idénticos a aquellos descritos con las Fórmulas I y II, excepto por el hecho de que uno o más átomos están sustituidos con uno o más átomos que tienen un número atómico o masa atómica específica. Los ejemplos de isótopos que se pueden incorporar en compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, azufre, flúor y cloro tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C ^{15}N, ^{18}O, ^{18}F y ^{36}Cl respectivamente. Los compuestos de la presente invención, profármacos de los mismos y sales farmacéuticamente aceptables de los compuestos o de los profármacos que contienen los isótopos mencionados anteriormente y/o otros isótopos de otros átomos están dentro del alcance de esta invención. Ciertos compuestos marcados con isótopos de la invención, por ejemplo, aquellos en los que se ha incorporado isótopos radiactivos tales como ^{3}H y ^{14}C, son útiles en los ensayos de distribución de fármacos en sustratos y/o tejidos. Los isótopos tritio (*es decir*, ^{3}H) y carbono-14 (*es decir*, ^{14}C) se prefieren particularmente por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio (*es decir*, ^{2}H) puede producir ciertas ventajas terapéuticas como resultado de la mayor estabilidad metabólica, por ejemplo, mayor vida media *in vivo* o menores requerimientos de dosificación y por tanto, se pueden preferir en algunas circunstancias. Los compuestos marcados con isótopos de esta invención y los profármacos de los mismos se pueden preparar generalmente

realizando los procedimientos descritos en los Esquemas y/o en los Ejemplos a continuación, sustituyendo un reactivo marcado con isótopos fácilmente disponible por un reactivo que no se ha marcado con isótopos.

En esta memoria descriptiva y en las reivindicaciones que siguen a continuación, se hará referencia a varios términos que se definirán para tener los siguientes significados:

Como se usa en este documento, el término mamíferos significa todos los mamíferos que contienen CETP en su plasma, por ejemplo, conejos y primates tales como monos y seres humanos, incluyendo mujeres y hombres. Otros mamíferos, por ejemplo perros, gatos, vacas, cabras, ovejas y caballos no tienen CETP en su plasma y por tanto, no están incluidos en este término.

El término "tratando", "tratar" o "tratamiento" como se usa en este documento incluye el tratamiento preventivo (por ejemplo, profiláctico) y paliativo.

El término "farmacéuticamente aceptable" significa que el vehículo, diluyente, excipiente y/o sal deben ser compatible con los demás ingredientes de la formulación y no debe ser perjudicial para el receptor del mismo.

Cuando se usa el término "compuestos" en este documento se incluye cualquier derivado o variación "farmacéuticamente aceptable", incluyendo isómeros conformacionales (por ejemplo, isómeros cis y trans) y todos los isómeros ópticos (por ejemplo, enantiómeros y diasterómeros), mezclas racémicas, diastereoméricas y otras mezclas de tales isómeros, así como solvatos, hidratos, isomorfos, polimorfos, tautómeros, ésteres, formas de sal y profármacos. "Tautómeros" significa compuestos químicos que pueden existir en dos o más formas de estructura diferente (isómeros) en equilibrio, diferenciándose las formas normalmente en la posición de un átomo de hidrógeno. Se pueden producir diversos tipos de tautomería, incluyendo tautomería

ceto-enol, anillo-cadena y anillo-anillo. La expresión "profármaco" se refiere a compuestos que son precursores de fármacos que después de la administración, liberan el fármaco *in vivo* mediante algún proceso químico o fisiológico (por ejemplo, al llevar un profármaco a pH fisiológico o por acción enzimática se convierte en la forma de fármaco deseada). Los profármacos ejemplares al escindirse liberan el ácido libre correspondiente y tales restos hidrolizables que forman ésteres de la presente invención incluyen, sin limitación, aquellos que tienen un resto carbonilo en el que el hidrógeno libre se reemplaza con alquilo (C_1-C_4), alcanoiloximetilo (C_2-C_7), 1-(alcanoiloxi)etilo que tiene de 4 a 9 átomos de carbono, 1-metil-1-(alcanoiloxi)etilo con 5 a 10 átomos de carbono, alcoxicarboniloximetilo con 3 a 6 átomos de carbono, 1-(alcoxicarboniloxi)etilo con 4 a 7 átomos de carbono, 1-metil-1-(alcoxicarboniloxi)etilo con 5 a 8 átomos de carbono, N-(alcoxicarbonil)aminometilo con 3 a 9 átomos de carbono, 1-(N-(alcoxicarbonil)amino)etilo con 4 a 10 átomos de carbono, 3-ftalidilo, 4-crotonolactonilo, gamma-butirolacton-4-ilo, di-N,N-alquilamino (C_1-C_2)alquilo (C_2-C_3) (tal como β-dimetilaminoetilo), carbamoil-alquilo (C_1-C_2), N,N-di-alquilcarbamoil(C_1-C_2)-alquilo (C_1-C_2) y piperidino-, pirrolidino- o morfolin-alquilo (C_2-C_3).

Los siguientes párrafos describen ejemplos de anillos para las descripciones del anillo genérico contenidas en este documento.

Los ejemplos de anillos aromáticos de cinco a seis miembros que tienen opcionalmente uno o dos heteroátomos seleccionados independientemente entre oxígeno, nitrógeno y azufre incluyen fenilo, furilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, piridinilo, piridinazinilo, pirimidinilo y pirazinilo.

Ejemplos de anillos de cinco a ocho miembros parcialmente saturados, totalmente saturados o totalmente insaturados que tienen opcionalmente de uno a cuatro

heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno incluyen ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y fenilo. Otros ejemplos de anillos de cinco miembros incluyen 2H-pirrolilo, 3H-pirrolilo, 2-pirrolinilo, 3-pirrolinilo, pirrolidinilo, 1,3-dioxolanilo, oxazolilo, tiazolilo, imidazolilo, 2H-imidazolilo, 2-imidazolinilo, imidazolidinilo, pirazolilo, 2-pirazolinilo, pirazolidinilo, isoxazolilo, isotiazolilo, 1,2-ditiolilo, 1,3-ditiolilo, 3H-1,2-oxatiolilo, 1,2,3-oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,3,4-tiadiazolilo, 1,2,3,4-oxatriazolilo, 1,2,3,5-oxatriazolilo, 3H-1,2,3-dioxazolilo, 1,2,4-dioxazolilo, 1,3,2-dioxazolilo, 1,3,4-dioxazolilo, 5H-1,2,5-oxatiazolilo y 1,3-oxatiolilo.

Otros ejemplos de anillos de seis miembros incluyen 2H-piranilo, 4H-piranilo, piridinilo, piperidinilo, 1,2-dioxinilo, 1,3-dioxinilo, 1,4-dioxanilo, morfolinilo, 1,3-ditianilo, tiomorfolinilo, piridazinilo, pirimidinilo, pirazinilo, piperazinilo, 1,3,5-triazinilo, 1,2,4-triazinilo, 1,2,3-triazinilo, 1,3,5-tritianilo, 4H-1,2-oxazinilo, 2H-1,3-oxazinilo, H-1,3-oxazinilo, 6H-1,2-oxazinilo, 1,4-oxazinilo, 2H-1,2-oxazinilo, 4H-1,4-oxazinilo, 1,2,5-ixotiazinilo, 1,4-oxazinilo, o-isoxazinilo, p-isoxazinilo, 1,2,5-oxatiazinilo, 1,2,6-oxatiazinilo, 1,4,2-oxadiazinilo y 1,3,5,2-oxadiazinilo.

Otros ejemplos de anillos de siete miembros incluyen azepinilo, oxepinilo y tiepinilo.

Otros ejemplos de anillos de ocho miembros incluyen ciclooctilo, ciclooctenilo y ciclooctadienilo.

Los ejemplos de anillos bicíclicos que constan de dos anillos condensados de cinco o seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno

incluyen indolizinilo, indolilo, isoindolilo, 3H-indolilo, 1H-isoindolilo, indolinilo, ciclopenta(b)piridinil, pirano(3,4-b)pirrolilo, benzofurilo, isobenzofurilo, benzo(b)tienilo, benzo(c)tienilo, 1H-indazolilo, indoxazinilo, benzoxazolilo, bencimidazolilo, benzotiazolilo, purinilo, 4H-quinolizinilo, quinolinilo, isoquinolinilo, cinolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, 1,8-naftiridinilo, pteridinilo, indenilo, isoindenilo, naftilo, tetralinilo, decalinilo, 2H-1-benzopiranilo, pirido(3,4-b)-piridinilo, pirido (3,2-b)-piridinilo, pirido(4,3-b)-piridinilo, 2H-1,3-benzoxazinilo, 2H-1,4-benzoxazinilo, 1H-2,3-benzoxazinilo, 4H-3,1-benzoxazinilo, 2H-1,2-benzoxazinilo y 4H-1,4-benzoxazinilo.

El término "alquileno" significa un hidrocarburo saturado (cadena lineal o ramificada) en el que se retira un átomo de hidrógeno de cada uno de dos carbonos adyacentes. Algunos ejemplos de tales grupos (suponiendo que la longitud designada abarca el ejemplo particular) son metileno, etileno, propileno, butileno, pentileno, hexileno, heptileno).

El término "halo" o "halógeno" significa cloro, bromo, yodo o flúor.

El término "alquilo" significa un hidrocarburo saturado de cadena lineal o un hidrocarburo saturado de cadena ramificada. Algunos ejemplos de tales grupos alquilo (suponiendo que la longitud designada abarca al ejemplo particular) son metilo, etilo, propilo, isopropilo, butilo, sec-butilo, butilo terciario, pentilo, isopentilo, neopentilo, pentilo terciario, 1-metilbutilo, 2-metilbutilo, 3-metilbutilo, hexilo, isohexilo, heptilo y octilo.

El "alquenilo" al que se hace referencia en este documento puede ser lineal o ramificado y también puede ser cíclico (por ejemplo, ciclobutenilo, ciclopentenilo, ciclohexenilo) o bicíclico o contener grupos cíclicos. Contiene 1-3 enlaces dobles carbono-carbono, que pueden ser cis o trans.

El término "alquiloxi" significa alquilo saturado de cadena lineal o alquilo saturado de cadena ramificada unido mediante un oxi. Algunos ejemplos de tales grupos alcoxi (suponiendo que la longitud designada abarca al ejemplo particular) son metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, butoxi terciario, pentoxi, isopentoxi, neopentoxi, pentoxi terciario, hexoxi, isohexoxi, heptoxi y octoxi.

Como se usa en este documento, el término "mono-N-" o "di-N,N-alquilo (C_1-C_x) se refiere al resto alquilo (C_1-C_x) tomado independientemente cuando es di-N,N-alquil(C_1-C_x) (x es un número entero).

Las referencias (por ejemplo, reivindicación 1) a "dicho carbono" en la frase "estando dicho carbono opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono mono-sustituido con hidroxi, estando dicho carbono opcionalmente sustituido con oxo" hace referencia a cada uno de los carbonos en la cadena carbonada incluyendo al carbono de unión.

Las referencias a "nitrógeno ... di-sustituido con oxo" de este documento (por ejemplo, en la reivindicación 1) se refieren a un nitrógeno terminal que constituye una funcionalidad nitro.

Debe apreciarse que si se puede unir o acoplar de otra forma un resto carbocíclico o heterocíclico a un sustrato designado mediante distintos átomos del anillo sin denotar un punto específico de unión, entonces se pretende incluir todos los puntos posibles, tanto a través de un átomo de carbono o, por ejemplo, un átomo de nitrógeno trivalente. Por ejemplo, el término "piridilo" significa 2-, 3- o 4-piridilo., el término "tienilo" significa 2- o 3-tienilo, etc.

DTT significa ditiotreitol. DMSO significa dimetilsulfóxido. EDTA significa ácido etilendiamintetraacético.

Como se usan en este documento, las expresiones "disolvente inerte a la

reacción" y "disolvente inerte" hacen referencia a un disolvente o mezcla de disolventes que no interactúa con los materiales de partida, reactivos, intermedios o productos en una forma que afecte de forma adversa al rendimiento del producto deseado.

En una realización de compuestos de fórmula I de la presente invención,

J es carbono;

R^1 es W-X;

W es carbonilo;

X es O-Y;

Y para cada caso es independientemente alquilo (C_1-C_6), teniendo opcionalmente dicho alquilo(C_1-C_6) de uno a nueve átomos de flúor o dicho alquilo (C_1-C_6) opcionalmente mono-sustituido con Z;

donde Z es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a seis miembros que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente Z está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), alquiltio (C_1-C_4), nitro, ciano, oxo o alquiloxicarbonilo (C_1-C_4), estando dicho alquilo (C_1-C_4) o alcoxi (C_1-$_4$) opcionalmente sustituido con uno a nueve átomos de flúor;

R^2 es beta y es una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada (C_1-C_4) lineal o ramificada, donde cada carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con un heteroátomo seleccionado independientemente entre oxígeno y azufre y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicha cadena carbonada opcionalmente mono-sustituida con oxo o hidroxi, estando dicho azufre opcionalmente mono- o di-sustituido con oxo; o dicho R^2 es un anillo parcialmente saturado, totalmente

saturado o totalmente insaturado de tres a cinco miembros que tiene opcionalmente un heteroátomo seleccionado independientemente entre oxígeno y azufre;

donde dicho anillo R^2 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), amino, nitro, alquiloxicarbonilo (C_1-C_4) o carboxi;

donde R^3 es una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, donde cada carbono, distinto de C4a puede reemplazarse opcionalmente con un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con ciano, estando dicho carbono opcionalmente mono-sustituido con oxo o nitrógeno, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo y estando dicha cadena carbonada opcionalmente mono, di- o tri-sustituida con V en C4a en el carbono R^3 adyacente a C4a; V es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres, cuatro, cinco o seis miembros que tiene opcionalmente de uno o tres heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno tal que V no es imidazolilo o un anillo heterocíclico totalmente saturado que contiene nitrógeno donde el nitrógeno del anillo está unido al grupo R^3;

donde dicho anillo V está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxicarbonilo (C_1-C_6), nitro, ciano u oxo, donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

R^4 es hidrógeno;

Cada uno de R^5 y R^6 son independientemente hidrógeno, halo, T, alcoxi (C_1-C_6) o alquilo (C_1-C_6), teniendo opcionalmente dicho sustituyente alcoxi (C_1-C_6) o alquilo (C_1-C_6) de uno a nueve átomos de flúor o estando dicho alcoxi (C_1-C_6) o alquilo (C_1-C_6) opcionalmente mono-sustituido con T;

donde T es un anillo de cinco a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente T está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor; y

R^7 es hidrógeno;

En otra realización de compuestos de fórmula I de la presente invención,

Y es alquilo (C_1-C_4), donde dicho sustituyente alquilo (C_1-C_4) tiene opcionalmente de uno a nueve átomos de flúor;

R^2 es alquilo (C_1-C_4), ciclopropilo o ciclobutilo;

R^3 es -(alquilo (C_1-C_4))(NH_2)(V), -(alquil (C_1-C_3))(NH(alquil (C_1-C_2))(V), -(alquil (C_1-C_4))(OH)(V), -(alquil (C_1-C_4))(F)(V), -(alquil (C_1-C_2)(O-C(O)alquil (C_1-C_2)(V), -C(O)-V, -C(OH)(C(O)O(alquil (C_1-C_3)(V), -CF_2(V), -(alquil (C_1-C_2))(NHC(O)alquil (C_1-C_2))(V), -CH_2(V), -(alquil (C_1-C_2))(C(O)O(alquil (C_1-C_2)(V), -(alquil (C_1-C_4))(C(O)NH_2(V), -(alquil (C_1-C_4))(CN)(V) o -(alquil (C_1-C_3))(alcoxi (C_1-C_3))(V),

V es fenilo opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), nitro, ciano u oxo donde dicho

sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

Cada uno de R^5 y R^6 son independientemente hidrógeno, halo, alcoxi (C_1-C_3) o alquilo (C_1-C_6), teniendo opcionalmente dicho sustituyente alcoxi (C_1-C_3) de uno a siete átomos de halógeno, teniendo opcionalmente dicho alquilo (C_1-C_6) de uno a nueve átomos de halógeno;

En otra realización de compuestos de fórmula I de la presente invención

Y es metilo, etilo, 1-propilo, 2-propilo o terc-butilo;

R^2 es metilo, etilo, 2-propilo, ciclopropilo o ciclobutilo;

R^3 es -C(O)-V, -C(OH)(C(O)OCH_3)(V), -CH(F)(V), -CF_2(V), -CH(OCH_3)(V), -CH(C(O)OCH_3)(V), -CH(CN)(V), -CH(OH)(V), -CH_2(V), -CH(NH_2)(V), -CH(NH(CH_3)(V), -CH(C(O)NH_2)(V), -CH(CH_2OH)(V), -CH(CH_2OCH_3)V, -CH($CH_2OC(O)CH_3$)V, -CH(CH_2F)V o -CH(CH_2NH_2)V; y

V es fenilo opcionalmente mono-, di- o tri-sustituido independientemente con halo, nitro o alquilo (C_1-C_2) donde dicho sustituyente alquilo (C_1-C_2) tiene opcionalmente de uno a nueve átomos de flúor;

Cada uno de R^5 y R^6 son independientemente hidrógeno, metilo, metoxi o cloro; teniendo opcionalmente dicho metoxi de uno a tres átomos de flúor, teniendo opcionalmente dicho metilo de uno a tres átomos de flúor.

En otra realización de la presente invención, los compuestos de fórmula I incluyen sustituyentes en los que

Y es etilo;

R^2 es etilo o metilo;

R^3 es (3,5-bis-(trifluorometil)-fenil)-hidroxi-metoxicarbonil-metilo; (3,5-bis-trifluorometil-fenil)-metoxicarbonil-metilo; (3,5-bis-trifluorometil-fenil)-ciano-metilo, 3,5-

bis-trifluorometil-benzoílo; (3,5-bis-trifluometil-fenil)-hidroxi-metilo; (3,5-bis-trifluorometil-fenil)-fluoro-metilo; (3,5-bis-trifluorometil-fenil)-difluoro-metilo; (3,5-bis-(trifluorometil)-bencilo); (3,5-bis-trifluorometil-fenilcarboamoil)-metilo; amino-(3,5-bis-(trifluorometil)-fenil)-metilo; (3,5-bis-(trifluorometil)-fenil)-metilamina-metilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-amino-etilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-fluoro-etilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-metoxi-etilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-hidroxi-etilo; o 2-acetoxi-1-(3,5-bis-(trifluorometil)-fenil)-etilo;

R^5 es metoxi o trifluorometilo; y

R^6 es hidrógeno o metoxi.

En otra realización de compuestos de fórmula I, el enlace entre C3 y J es un enlace sencillo.

En otra realización más de compuestos de fórmula I, el enlace entre C3 y J es un enlace doble.

En otra realización, los compuestos de fórmula I se seleccionan entre el grupo compuesto por:

Éster etílico del ácido (*R*, *R*, *S*)-4-[Amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[Amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-(3,5-bis-trifluorometil-bencil)-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metilaminometil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metilaminometil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-

metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[2-Acetoxi-1-(3,5-bis-trifluorometil-fenil)-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[2-Acetoxi-1-(3,5-bis-trifluorometil-fenil)-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-metoxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-metoxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-fluoro-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-fluoro-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-amino-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-amino-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-(3,5-bis-trifluorometil-benzoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-(3,5-bis-trifluorometil-benzoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-

dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico; y

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal o profármaco farmacéuticamente aceptable del mismo.

En otra realización de compuestos de fórmula I de la presente invención,

J es nitrógeno;

el enlace entre C3 y J es un enlace sencillo;

R^1 es W-X;

W es carbonilo;

X es -O-Y;

Y para cada caso es independientemente alquilo (C_1-C_6), teniendo opcionalmente dicho alquilo(C_1-C_6) de uno a nueve átomos de flúor o estando dicho alquilo (C_1-C_6) opcionalmente mono-sustituido con Z;

donde Z es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a seis miembros que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente Z está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), alquiltio (C_1-C_4), nitro, ciano, oxo o alquiloxicarbonilo (C_1-C_4), estando dicho alquilo (C_1-C_4) o alcoxi (C_1-C_4) opcionalmente sustituido con uno a nueve átomos de flúor;

R^2 es una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada (C_1-C_4), lineal o ramificada, donde cada carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con un heteroátomo seleccionado independientemente entre oxígeno y azufre y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicha cadena carbonada opcionalmente mono-sustituida con oxo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho azufre opcionalmente mono- o di-sustituido con oxo,; o dicho R^2 es un anillo parcialmente saturado, totalmente saturado o totalmente

insaturado de tres a cinco miembros que tiene opcionalmente un heteroátomo seleccionado independientemente entre oxígeno y azufre; donde dicho anillo R^2 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), amino, nitro, alquiloxicarbonilo (C_1-C_4) o carboxi;

R^3 es una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, donde cada carbono, distinto de C4a o del carbono R^3 adyacente a C4a, puede reemplazarse opcionalmente con un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono, distinto de C4a, opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con ciano, estando dicho carbono opcionalmente mono-sustituido con oxo o nitrógeno, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo y estando opcionalmente dicha cadena carbonada mono, di- o tri-sustituida con V en C4a en el carbono R^3 adyacente a C4a;

V es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de cinco o seis miembros que tiene opcionalmente de uno o tres heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno tal que V no es imidazolilo o un anillo heterocíclico totalmente saturado que contiene nitrógeno donde el nitrógeno del anillo está unido al grupo R^3; donde dicho anillo V está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxicarbonilo (C_1-C_6), nitro, ciano u oxo, donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

R^4 es hidrógeno;

Cada uno de R^5 y R^6 son independientemente hidrógeno, halo, T, alcoxi (C_1-C_6) o alquilo (C_1-C_6), teniendo opcionalmente dicho sustituyente alcoxi (C_1-C_6) o alquilo (C_1-C_6) de uno a nueve átomos de flúor o estando dicho alcoxi (C_1-C_6) o alquilo (C_1-C_6) opcionalmente mono-sustituido con T;

donde T es un anillo de cinco a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente T está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

R^7 es hidrógeno;

En otra realización de compuestos de fórmula I de la presente invención,

Y es alquilo (C_1-C_4), donde dicho sustituyente alquilo (C_1-C_4) tiene opcionalmente de uno a nueve átomos de flúor;

R^2 es alquilo (C_1-C_4), ciclpropilo o ciclobutilo;

R^3 es -C(O)-V, -CH(C(O)O(alquil (C_1-C_3))(V) o -CH(CN)(V);

V es fenilo opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), nitro, ciano u oxo donde dicho sustituyente alquilo (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

Cada uno de R^5 y R^6 son independientemente hidrógeno, alcoxi (C_1-C_3) o alquilo (C_1-C_6), teniendo opcionalmente dicho sustituyente alcoxi (C_1-C_3) de uno a nueve átomos de flúor, teniendo dicho sustituyente alquilo (C_1-C_6) opcionalmente de uno a siete átomos de flúor;

o una sal farmacéuticamente aceptable del mismo.

En otra realización de compuestos de fórmula I de la presente invención

Y es metilo, etilo, 1-propilo, 2-propilo o terc-butilo;

R^2 es metilo, etilo, 2-propilo, ciclopropilo o ciclobutilo;

R^3 es 3,5-bis-trifluorometil-benzoílo, (3,5-bis-trifluorometil-fenil)-ciano-metilo o (3,5-bis-trifluorometil-fenil)-metoxicarbonil-metilo;

R^5 es metilo o trifluorometilo;

R^6 es hidrógeno o metilo.

En otra realización de compuestos de fórmula I, los compuestos se seleccionan entre el grupo compuesto por:

Éster etílico del ácido (*R*)-4-[(3,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster metílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster metílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster isopropílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-

metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster isopropílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinoxalin-1-carboxílico;

o una sal o profármaco farmacéuticamente aceptable del mismo.

Además, una realización de la presente invención incluye un procedimiento para tratar la aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio en un mamífero administrando a un mamífero en necesidad de tal tratamiento una cantidad para tratar la aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio de un compuesto de fórmula I o II, o un profármaco del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco.

En otra realización, se trata la aterosclerosis.

En otra realización, se trata la enfermedad vascular periférica.

En otra realización, se trata la dislipidemia.

En otra realización, se trata la hiperbetalipoproteinemia.

En otra realización, se trata la hipoalfalipoproteinemia.

En otra realización, se trata la hipercolesterolemia familiar.

En otra realización, se trata la enfermedad de la arteria coronaria.

En otra realización, se trata el infarto de miocardio.

Además, la presente invención incluye una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de fórmula I o II, un profármaco del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco y un vehículo, diluyente o excipiente farmacéuticamente aceptable.

En una realización, al presente invención es una composición farmacéutica para el tratamiento de la aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio en un mamífero que comprende una cantidad terapéuticamente eficaz de compuesto de fórmula I o II, un profármaco del mismo o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco y un vehículo, diluyente o excipiente farmacéuticamente aceptable.

En otra realización, la presente invención es una composición farmacéutica para el tratamiento de la aterosclerosis en un mamífero que comprende una cantidad para tratar la aterosclerosis de un compuesto de fórmula I o II, un profármaco del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco y un vehículo, diluyente o excipiente farmacéuticamente aceptable.

En otra realización, la presente invención es una composición de combinación farmacéutica que comprende: una cantidad terapéuticamente eficaz de una composición que comprende: un primer compuesto, siendo dicho primer compuesto un compuesto de fórmula I o II, un profármaco del mismo o una sal farmacéuticamente aceptable de

dicho compuesto o de dicho profármaco; un segundo compuesto, siendo dicho segundo compuesto un inhibidor de la HMG-CoA reductasa, un inhibidor de la secreción de MTP/Apo B, un modulador de PPAR, un inhibidor de la recaptación de ácidos biliares, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, niacina de liberación lenta, una combinación de niacina y lovastatina, una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT o un secuestrador de ácidos biliares y un vehículo, diluyente o excipiente farmacéuticamente aceptable.

En otra realización, la presente invención incluye una composición de combinación farmacéutica donde el segundo compuesto en un inhibidor de la HMG-CoA reductasa o un modulador de PPAR.

En otra realización, la presente invención incluye una composición de combinación farmacéutica donde el segundo compuesto en lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, rosuvastatina o pitavastatina.

En otra realización, la presente invención incluye una composición de combinación farmacéutica que comprende adicionalmente un inhibidor de la absorción de colesterol. En otra realización, el inhibidor de la absorción de colesterol es ezetimibe.

Una realización de la presente invención incluye un procedimiento para tratar la aterosclerosis en un mamífero que comprende administrar a un mamífero en necesidad de tratamiento; un primer compuesto, siendo dicho primer compuesto un compuesto de fórmula I, un profármaco del mismo o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco; y un segundo compuesto, siendo dicho segundo compuesto un inhibidor de la HMG CoA reductasa, un modulador de PPAR, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, niacina de liberación lenta, una combinación de niacina y lovastatina,

una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT o un secuestrador de ácidos biliares; donde las cantidades del primer y segundo compuesto tienen como resultado un efecto terapéutico.

En otra realización, la presente invención incluye un procedimiento para tratar la aterosclerosis donde el segundo compuesto en un inhibidor de la HMG CoA reductasa o un modulador de PPAR.

En otra realización, la presente invención incluye un procedimiento para tratar la aterosclerosis donde el segundo compuesto es lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, rosuvastatina o pitavastatina.

En otra realización, la presente invención incluye un procedimiento para tratar la aterosclerosis donde el procedimiento comprende además un inhibidor de la absorción de colesterol. En otra realización, el inhibidor de la absorción de colesterol es ezetimibe.

Otra realización de la presente invención incluye un kit para conseguir un efecto terapéutico en un mamífero que comprende envasados conjuntamente con un primer agente terapéutico que comprende una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1, 8, 12 ó 13, un profármaco del mismo o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco y un vehículo farmacéuticamente aceptable, un segundo agente terapéutico que comprende una cantidad terapéuticamente eficaz de un inhibidor de la HMG CoA reductasa, un modulador de PPAR, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, niacina de liberación lenta, una combinación de niacina y lovastatina, una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT o un secuestrador de ácidos biliares y un vehículo farmacéuticamente aceptable e instrucciones para la administración de dicho primer y segundo agente para conseguir el efecto terapéutico.

En otra realización, la presente invención incluye un kit donde dicho segundo compuesto en un inhibidor de la HMG CoA reductasa o un modulador de PPAR.

En otra realización, la presente invención incluye un kit donde dicho segundo compuesto es lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, rosuvastatina o pitavastatina.

En otra realización, la presente invención incluye un kit que comprende adicionalmente un inhibidor de la absorción de colesterol. En otra realización, el inhibidor de absorción de colesterol es ezetimibe.

Los compuestos específicos de Fórmula III incluyen:

Éster etílico del ácido 2-etil-4-yodo-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido 4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido 4-bromo-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido 4-diazo-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido 4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1,4-dicarboxílico;

Éster 4-metílico, éster 1-etílico del ácido 2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1,4-dicarboxílico;

Éster etílico del ácido 2-etil-4-(metoxi-metil-carbamoil)-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster 4-metílico, éster 1-etílico del ácido 2-etil-6-trifluorometil-2H-quinolin-1,4-dicarboxílico;

Éster etílico del ácido 4-cloro-2-etil-4-metoxicarboncarbonil-6-trifluorometil-

3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido 2-etil-4-metoxicarboncarbonil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido 4-diazo-6,7-dimetoxi-2-metil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido 6,7-dimetoxi-4-metoxicarbocarbonil-2-metil-2H-quinolin-1-carboxílico;

Éster 4-metílico, éster 1-etílico del ácido 6,7-dimetoxi-2-metil-3,4-dihidro-2H-quinolin-1,4-dicarboxílico

Éster etílico del ácido 6,7-dimetoxi-4-(metoxi-metil-carbamoil)-2-metil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido 2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido 2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster metílico del ácido 2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster metílico del ácido 2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster 1-propílico del ácido 2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster 1-propílico del ácido 2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster 2-propílico del ácido 2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster 2-propílico del ácido 2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster terc-butílico del ácido 2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster terc-butílico del ácido 2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

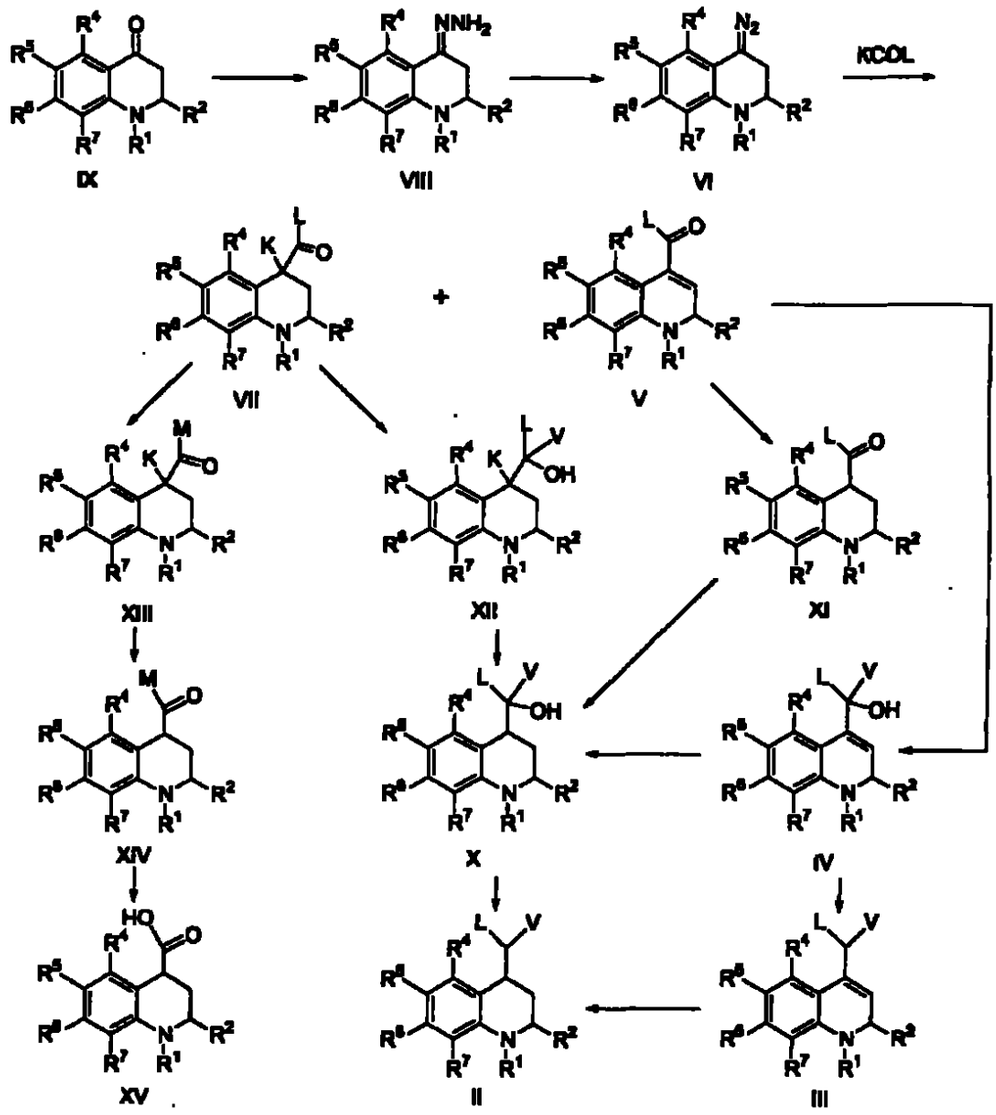
Éster 4-metílico, éster 1-etílico del ácido 2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1,4-dicarboxílico;

En general, los compuestos de esta invención se pueden fabricar con procesos que incluyen procesos análogos a los conocidos en la técnica química, particularmente a la vista de la descripción contenida en este documento. Ciertos procesos para la fabricación de los compuestos de esta invención se proporcionan como características adicionales de la invención y se ilustran mediante los siguientes esquemas de reacción. Otros procesos se describen en la sección experimental. Otros procesos análogos se describen en las siguientes patentes de Estados Unidos, que se incorporan por referencia en su totalidad en este documento: Patente de Estados Unidos 6.140.342; Patente de Estados Unidos 6.362.198; Patente de Estados Unidos 6.147.090; Patente de Estados Unidos 6.395.751; Patente de Estados Unidos 6.147.089; Patente de Estados Unidos 6.310.075; Patente de Estados Unidos 6.197.786; Patente de Estados Unidos 6.140.343; Patente de Estados Unidos 6.489.478 y en la Publicación Internacional N° WO 00/17164.

Los esquemas de reacción descritos en este documento pretenden proporcionar una descripción general de la metodología empleada en la preparación de muchos de los Ejemplos dados. Sin embargo, debe apreciarse en las descripciones detalladas que se dan en la sección Experimental que las formas de preparación empleadas abarcan más

que los procedimientos generales descritos en este documento. En particular, se apreciará que los compuestos preparados de acuerdo con estos Esquemas se pueden modificar adicionalmente para proporcionar nuevos Ejemplos dentro del alcance de esta invención. Por ejemplo, se puede hacer reaccionar adicionalmente una funcionalidad éster usando procedimientos conocidos por los especialistas en la técnica para dar otro éster, una amida, un carbinol o una cetona.

ESQUEMA 1



De acuerdo con el Esquema de Reacción 1, los compuestos deseados en los que J es carbono, el enlace doble opcional está ausente, R^3 es un grupo CH(V)(L) donde L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente (representado en el Esquema de Reacción 1 como compuestos de

Fórmula II) pueden prepararse en forma de una mezcla de diastereoisómeros a partir de los correspondientes compuestos del Esquema 1, Fórmula III por reducción del enlace doble o L es R^3 como se ha definido anteriormente. Esto puede conseguirse por hidrogenación en un disolvente inerte a la reacción tal como metanol, etanol o ácido acético con un catalizador tal como paladio o rodio sobre carbono en una presión de hidrógeno igual a 68,94-344,73 kPa (10-50 psi) durante un periodo comprendido entre 2-24 horas o mediante hidrogenación de transferencia usando formiato amónico en metanol a reflujo en presencia de un catalizador tal como paladio en carbono en un disolvente inerte a la reacción tal como metanol o etanol a una temperatura comprendida entre 0°C y 80°C, típicamente de 25°C a 60°C. Este procedimiento de preparación de estos compuestos particulares de Fórmula I típicamente proporciona una preponderancia de aquellos diastereoisómeros en los que los grupos R^2 y R^3 están en posición cis entre sí.

Los compuestos deseados de Fórmula III en los que L, V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de una mezcla de diastereoisómeros a partir de los compuestos correspondientes de Fórmula IV por retirada del grupo hidroxilo. Esto puede conseguirse por tratamiento con un agente de cloración tal como cloruro de fósforo (III) o cloruro de tionilo en un disolvente inerte a la reacción tal como cloruro de metileno o cloroformo conteniendo opcionalmente una base tal como piridina, diisopropiletilamina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. Después, el derivado de cloro formado de esta forma se trata con un metal finamente dividido tal como cinc en presencia de un ácido o mezcla de ácidos, tal como ácido acético o ácido clorhídrico en un disolvente adecuado, o mezcla de disolventes, tal como metanol, agua o tetrahidrofurano a una

temperatura comprendida entre 25°C y 60°C, típicamente a la temperatura ambiente, para proporcionar el producto deseado de Fórmula III.

Los compuestos deseados de Fórmula IV en los que L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de una mezcla de diastereoisómeros a partir de los compuestos correspondientes de Fórmula V por reacción con un derivado organometálico adecuado del grupo V tal como un derivado de magnesio o litio, preparado a su vez con un compuesto V-Hal donde Hal represente un átomo de cloro, bromo o yodo, usando procedimientos conocidos por los especialistas en la técnica, como se describe, por ejemplo, en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. Esta reacción se realiza en un disolvente inerte a la reacción tal como tetrahidrofurano o éter dietílico a una temperatura comprendida entre -78°C y 25°C, típicamente -78°C, para proporcionar el producto deseado de Fórmula IV.

Los compuestos deseados de Fórmula V en los que L es un grupo alcoxicarbonilo (C_1-C_6) y R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar a partir de los compuestos correspondientes de Fórmula VI por reacción con un compuesto acilo KCOL donde K es un grupo saliente tal como cloro o bromo, a una temperatura comprendida entre 0°C y 25°C, típicamente temperatura ambiente, en un disolvente inerte a la reacción tal como acetonitrilo o tolueno opcionalmente en presencia de una base tal como diisopropiletilamina o trietilamina para retirar las trazas de HK que puedan estar presentes. Dependiendo de la naturaleza de los sustituyentes en los compuestos de Fórmula VI y de la naturaleza de L, el compuesto de Fórmula V puede obtenerse en forma de mezcla con el correspondiente compuesto de Fórmula VII.

Los compuestos deseados de Fórmula VI en los que R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar a partir de los compuestos correspondientes de Fórmula VIII por reacción con un agente oxidante adecuado, típicamente óxido de manganeso (IV) en un disolvente inerte a la reacción tal como éter dietílico a una temperatura comprendida entre 0ºC y 25ºC, típicamente temperatura ambiente. Como esta reacción produce un equivalente de agua, que puede ser perjudicial para la etapa posterior, éste se puede retirar opcionalmente por adición de un disolvente adecuado para la siguiente reacción tal como acetonitrilo o tolueno y evaporación de la mezcla de disolventes a un volumen algo menor que el del disolvente añadido, pero no a sequedad.

Los compuestos deseados de Fórmula VIII en los que R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar a partir de los compuestos correspondientes de Fórmula IX por reacción con hidrato de hidracina en un disolvente inerte a la reacción tal como etanol o tolueno a una temperatura comprendida entre 25ºC y 180ºC, típicamente de 80ºC a 170ºC. La formación de hidrazona se puede facilitar con la retirada continua de agua, tal como con el uso de un aparato Dean-Stark, o calentando en un recipiente cerrado a una temperatura superior al punto de ebullición del disolvente tal como con un horno microondas.

Una preparación alternativa de los compuestos deseados de Fórmula II donde L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden realizar a partir de los compuestos correspondientes de Fórmula X por tratamiento con un agente de cloración tal como cloruro de fósforo (III) o cloruro de tionilo en un disolvente inerte a la reacción tal como cloruro de metileno o cloroformo conteniendo opcionalmente una base tal como piridina, diisopropiletilamina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0ºC y 60ºC,

típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. Después, el derivado de cloro formado de esta forma como una mezcla de diastereoisómeros se trata con un metal finamente dividido tal como cinc en presencia de un ácido o mezcla de ácidos, tal como ácido acético o ácido clorhídrico en un disolvente adecuado, o mezcla de disolventes, tal como metanol, agua o tetrahidrofurano a una temperatura comprendida entre 25°C y 60°C, típicamente temperatura ambiente, para proporcionar el producto deseado de Fórmula II.

Los compuestos deseados de Fórmula X donde L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de mezcla de diasterómeros a partir de los compuestos correspondientes de Fórmula XI por reacción con un derivado organometálico adecuado del grupo V tal como un derivado de magnesio o litio, preparado a su vez con un compuesto V-Hal donde Hal represente un átomo de cloro, bromo o yodo, usando procedimientos conocidos por los especialistas en la técnica, como se describe, por ejemplo, en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. Esta reacción se realiza en un disolvente inerte a la reacción tal como tetrahidrofurano o éter dietílico a una temperatura comprendida entre -78°C y 25°C, típicamente -78°C, para proporcionar el producto deseado de Fórmula X.

Los compuestos deseados de Fórmula XI donde L es un grupo alcoxicarbonilo (C_1-C_6) y R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de mezcla de diasterómeros a partir de los compuestos correspondientes de Fórmula V por reducción del enlace doble. Esto puede conseguirse por hidrogenación en un disolvente inerte a la reacción tal como metanol, etanol o ácido acético con un catalizador tal como paladio o rodio sobre carbono en una presión de

hidrógeno igual a 68-345 kPa durante un periodo comprendido entre 2-24 horas o mediante hidrogenación de transferencia usando formiato amónico en metanol a reflujo en presencia de un catalizador tal como paladio en carbono en un disolvente inerte a la reacción tal como metanol o etanol a una temperatura comprendida entre 0°C y 80°C, típicamente 25°C a 60°C.

Una preparación alternativa de los compuestos deseados de Fórmula X donde L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de mezcla de diasterómeros a partir de los compuestos correspondientes de Fórmula XII por, donde K es un grupo saliente tal como cloro o bromo , por hidrogenación en un disolvente inerte a la reacción tal como metanol, etanol o ácido acético con un catalizador tal como paladio o rodio sobre carbono en una presión de hidrógeno igual a 68-345 kPa durante un periodo comprendido entre 2-24 horas o mediante hidrogenación de transferencia usando formiato amónico en metanol a reflujo en presencia de un catalizador tal como paladio en carbono en un disolvente inerte a la reacción tal como metanol o etanol a una temperatura comprendida entre 0°C y 80°C, típicamente 25°C a 60°C para proporcionar el producto deseado de fórmula X.

Otra preparación alternativa de los compuestos deseados de Fórmula X donde L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se puede preparar en forma de mezcla de diasterómeros a partir de los compuestos correspondientes de Fórmula IV por reducción del enlace doble. Esto puede conseguirse por hidrogenación en un disolvente inerte a la reacción tal como metanol, etanol o ácido acético con un catalizador tal como paladio o rodio sobre carbono en una presión de hidrógeno igual a 103-345 kPa durante un periodo comprendido entre 2-24 horas o mediante hidrogenación de transferencia usando

formiato amónico en metanol a reflujo en presencia de un catalizador tal como paladio en carbono en un disolvente inerte a la reacción tal como metanol o etanol a una temperatura comprendida entre 0°C y 80°C, típicamente 25°C a 60°C para proporcionar el producto deseado de Fórmula X. Un procedimiento alternativo de reducción implica tratamiento con diimida que se genera in situ en un disolvente inerte a la reacción en presencia de los compuestos de Fórmula IV mediante varios procedimientos conocidos por los especialistas en la técnica, tales como aquellos descritos en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995.

Los compuestos deseados de Fórmula XII en los que L es un grupo alcoxicarbonilo (C_1-C_6), K es un grupo saliente tal como cloro o bromo y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de una mezcla de diastereoisómeros a partir de los compuestos correspondientes de Fórmula VII por reacción con un derivado organometálico adecuado del grupo V tal como un derivado de magnesio o litio, preparado a su vez con un compuesto V-Hal donde Hal representa un átomo de cloro, bromo o yodo. Esta reacción se realiza en un disolvente inerte a la reacción tal como tetrahidrofurano o éter dietílico a una temperatura comprendida entre -78°C y 25°C, típicamente -78°C, para proporcionar el producto deseado de Fórmula XII.

Como se ha descrito anteriormente, los compuestos deseados de Fórmula VII en los que L es un grupo alcoxicarbonilo (C_1-C_6), K es un grupo saliente tal como cloro o bromo y R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de una mezcla de diastereoisómeros a partir de los compuestos correspondientes de Fórmula VI por reacción con un compuesto acilo KCOL a una temperatura comprendida entre 0°C y 25°C, típicamente temperatura ambiente, en un

disolvente inerte a la reacción tal como acetonitrilo o tolueno opcionalmente en presencia de una base tal como diisopropiletilamina o trietilamina para retirar las trazas de HK que puedan estar presentes. Dependiendo de la naturaleza de los sustituyentes en los compuestos de Fórmula VI y de la naturaleza de L, el compuesto de Fórmula VII puede obtenerse en forma de mezcla con el correspondiente compuesto de Fórmula V.

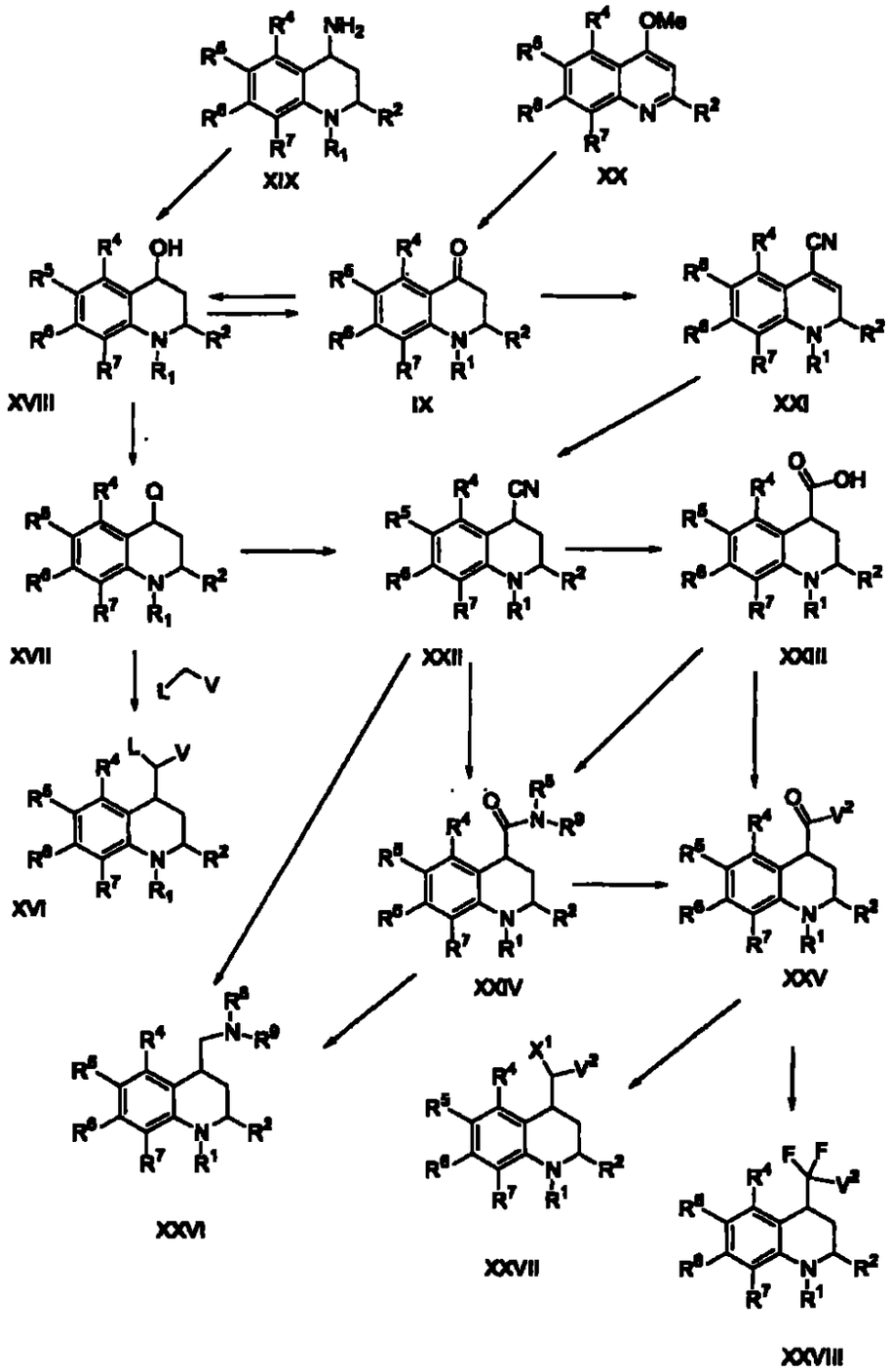
Los compuestos deseados de Fórmula XIII en los que M es un grupo alcoxi (C_1-C_6) y R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de una mezcla de diastereoisómeros a partir de los compuestos correspondientes de Fórmula VI por reacción con fosgeno a una temperatura comprendida entre 0°C y 25°C, típicamente temperatura ambiente, en un disolvente inerte a la reacción tal como acetonitrilo o tolueno en presencia de una base tal como diisopropiletilamina o trietilamina. La adición del alcohol deseado MOH al cloruro ácido en presencia de un exceso de base proporciona el compuesto deseado de Fórmula XIII.

Los compuestos deseados de Fórmula XIV en los que M es un grupo alcoxi (C_1-C_6) y R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar en forma de una mezcla de diastereoisómeros a partir de los compuestos correspondientes de Fórmula XIII por hidrogenólisis. Esto puede conseguirse por hidrogenación en un disolvente inerte a la reacción tal como metanol, etanol o ácido acético con un catalizador tal como paladio o rodio sobre carbono en una presión de hidrógeno igual a 103-345 kPa durante un periodo comprendido entre 2-24 horas o mediante hidrogenación de transferencia usando formiato amónico en metanol a reflujo en presencia de un catalizador tal como paladio en carbono en un disolvente inerte a la reacción tal como metanol o etanol a una temperatura comprendida entre 0°C y 80°C, típicamente 25°C a 60°C. Alternativamente, los compuestos de Fórmula XIII se pueden

tratar con un metal finamente dividido tal como cinc en presencia de un ácido o mezcla de ácidos, tal como ácido acético o ácido clorhídrico en un disolvente adecuado, o mezcla de disolventes, tal como metanol, agua o tetrahidrofurano a una temperatura comprendida entre 25°C y 60°C, típicamente temperatura ambiente, para proporcionar el producto deseado de Fórmula XIV.

Los compuestos deseados de Fórmula XV en los que R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente se pueden preparar por hidrólisis del grupo éster de los compuestos de Fórmula XIV, usando procedimientos conocidos por los especialistas en la técnica, tales como los que se pueden encontrar en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, por ejemplo, por tratamiento con una base acuosa, preferiblemente hidróxido de litio, sodio o potasio en un disolvente polar, preferiblemente dioxano, a una temperatura comprendida entre 0°C y 100°C (preferiblemente temperatura ambiente) durante un periodo comprendido entre 1 y 20 horas para proporcionar los compuestos deseados de Fórmula XV.

ESQUEMA 2


XIX
XX
XVIII
IX
XXI
XVII
XXII
XXIII
XVI
XXIV
XXV
XXVI
XXVII
XXVIII

De acuerdo con el Esquema de Reacción 2, los compuestos deseados en los que J es carbono, el enlace doble opcional está ausente, R^3 es un grupo CH(V)(L) donde L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente (representados como compuestos de Fórmula XVI) pueden prepararse en forma de una mezcla de diastereoisómeros a partir de los correspondientes compuestos de Fórmula XVII por reacción con un compuesto VCH_2L en presencia de una base adecuada tal como 1,8-diazabiciclo[5.4.0]undec-7-eno, diisopropiletilamina, trietilamina o hidruro sódico en un disolvente inerte a la reacción tal como N,N-dimetilformamida, dimetilsulfóxido, acetonitrilo o tolueno a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente.

Los compuestos deseados de Fórmula XVII donde Q es un grupo saliente tal como cloro, bromo, metanosulfoniloxi o p-toluenosulfoniloxi y R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse en forma de una mezcla de diastereoisómeros a partir de los correspondientes compuestos de Fórmula XVIII por reacción con un reactivo apropiado tal como cloruro de metanosulfonilo o cloruro de toluenosulfonilo en presencia de una base adecuada tal como diisopropiletilamina o trietilamina en un disolvente inerte a la reacción tal como N,N-dimetilformamida, dimetilsulfóxido, cloroformo, cloruro de metileno o tolueno a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente. Otros reactivos adecuados para la formación de los compuestos de Fórmula XVII incluyen cloruro de fósforo (III), bromuro de fósforo (III) y cloruro de tionilo opcionalmente en un disolvente inerte a la reacción tal como cloroformo, cloruro de metileno, piridina o tolueno a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente.

Los compuestos deseados de Fórmula XVIII donde R^1, R^2, R^4, R^5, R^6 y R^7 son

como se han descrito anteriormente pueden prepararse en forma de una mezcla de diastereoisómeros a partir de los correspondientes compuestos de Fórmula IX por reducción del grupo carbonilo usando procedimientos y reactivos conocidos por los especialistas, tales como los que se pueden encontrar en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, por ejemplo, usando borohidruro sódico en un disolvente alcohol tal como metanol o etanol a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente o usando tri-sec-butilborohidruro potásico (K-Selectride®) en un disolvente inerte a la reacción tal como tetrahidrofurano o éter dietílico a una temperatura comprendida entre -78°C y 25°C, típicamente 0°C.

En un procedimiento alternativo, los compuestos deseados de Fórmula XVIII donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden obtenerse por tratamiento de los correspondientes compuestos de Fórmula XIX con nitrito sódico en presencia de un ácido, preferiblemente ácido acético, seguido de hidrólisis con una base adecuada tal como hidróxido de litio, sodio o potasio, preferiblemente hidróxido sódico en un disolvente hidroxílico adecuado tal como etanol para dar los compuestos deseados de Fórmula XIX. Los procedimientos para la preparación de compuestos de Fórmula XIX se describen en la Patente de Estados Unidos Nº 6197786 y en la Solicitud Internacional WO 0140190.

Los compuestos deseados de Fórmula IX donde R^1 es un grupo alquiloxicarbonilo y R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de 4-metoxiquinolina de Fórmula XX por tratamiento con un derivado de organomagnesio del grupo R^2 junto con un agente de acilación tal como cloroformiato de etilo a una temperatura comprendida entre -100°C y 70°C, típicamente -78°C en un disolvente inerte a la

reacción tal como tetrahidrofurano seguido de calentamiento a una temperatura comprendida entre 0°C y aproximadamente 70°C (preferiblemente temperatura ambiente) durante un periodo comprendido entre 0,1 y 24 horas, preferiblemente 1 hora, seguido de hidrólisis en un ácido acuoso, preferiblemente ácido clorhídrico 1 N para dar los compuestos deseados de Fórmula IX, como se describe en la Patente de Estados Unidos 6197786.

En un procedimiento alternativo, los compuestos deseados de Fórmula IX donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden obtenerse por oxidación de los correspondientes compuestos de Fórmula XVIII usando una diversidad de procedimientos y reactivos conocidos por los especialistas en la técnica, tales como los que se pueden encontrar en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, por ejemplo, clorocromato de piridinio, hipoclorito sódico acuoso en presencia de una cantidad catalítica del radical libre 2,2,6,6,-tetrametil-1-piperidiniloxi (TEMPO) y bromuro de potasio catalítico en un disolvente inerte a la reacción tal como cloruro de metileno o alternativamente con anhídrido acético y dimetilsulfóxido.

Los compuestos deseados de Fórmula XXI donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden obtenerse a partir de los compuestos de Fórmula IX por tratamiento con cianuro de trimetilsililo en un disolvente inerte tal como un hidrocarburo aromático (por ejemplo, benceno, tolueno, xileno) en presencia de una cantidad catalítica de ácido de Lewis, preferiblemente yoduro de cinc, a una temperatura de aproximadamente 25°C a aproximadamente 140°C, preferiblemente de aproximadamente 80°C a aproximadamente 100°C, durante 1-12 horas, preferiblemente 5 horas. Después, la solución resultante se concentra a sequedad y se añade directamente sin purificación adicional a un disolvente polar (por ejemplo, metanol,

etanol). Una solución de ácido (preferiblemente clorhídrico) en un disolvente polar aprótico (preferiblemente dioxano) se añade a la solución y la mezcla se agita a una temperatura comprendida entre 0ºC y aproximadamente 100ºC, preferiblemente temperatura ambiente, durante un periodo de 1-24 horas, preferiblemente 12 horas, para producir compuestos de Fórmula XXI.

Los compuestos de fórmula XXII deseados donde R^1, R^2, R^4, R^5, R^6, R^7 son como se han descrito anteriormente y pueden prepararse a partir de los compuestos correspondientes de fórmula XXI por tratamiento con un agente reductor tal como borohidruro sódico o cianoborohidruro sódico en un disolvente inerte a la reacción tal como metanol o etanol, preferiblemente etanol, a una temperatura de aproximadamente 0ºC a aproximadamente 100ºC (preferiblemente a la temperatura de reflujo) durante 0,1 a 5 horas (preferiblemente 0,75 horas) para proporcionar los compuestos deseados de fórmula XXII.

Alternativamente, los compuestos deseados de Fórmula XXII donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XVII, donde Q es un grupo saliente como se ha descrito anteriormente, por tratamiento con una sal de cianuro tal como litio, sodio, potasio o cianuro de tetraalquilamonio en un disolvente inerte a la reacción tal como dimetilformamida a una temperatura comprendida entre 0ºC y 100ºC durante un periodo de 1 a 12 horas, para proporcionar los compuestos de Fórmula XXII.

Los compuestos deseados de Fórmula XXIII donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXII por disolución en ácido sulfúrico concentrado que contiene cinco equivalentes de agua a una temperatura comprendida entre 0ºC y 100ºC (preferiblemente temperatura ambiente) durante un periodo de 1-20 horas. Después, la

amida resultante se disuelve en un disolvente polar (preferiblemente cloruro de metileno) y se trata con tetrafluoroborato de trimetiloxonio a una temperatura comprendida entre 0ºC y 100ºC (preferiblemente temperatura ambiente) durante 1-20 horas (preferiblemente 12 horas). Después, el éster imino resultante se trata con una base acuosa, preferiblemente hidróxido de litio, sodio o potasio en un disolvente polar, preferiblemente dioxano, a una temperatura comprendida entre 0ºC y 100ºC (preferiblemente temperatura ambiente) durante un periodo comprendido entre 1 y 20 horas para proporcionar los Compuestos de Fórmula XXIII.

Los compuestos deseados de Fórmula XXIV donde R^1, R^2, R^4, R^5, R^6, R^7, R^8 y R^9 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXIII tratando el ácido en un disolvente inerte a la reacción (preferiblemente diclorometano) con la correspondiente amina (NHR^8R^9) en presencia de hidrato de 1-hidroxibenzotriazol ((HOBT) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCl) a una temperatura comprendida entre 0ºC y 100ºC (preferiblemente a temperatura ambiente) durante un periodo comprendido entre 1 y 24 horas (preferiblemente 12 horas).

Los compuestos deseados de Fórmula XXV donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y V^2 es un grupo V o CH_2V donde V es como se ha descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXIV cuando R^8 es metilo y R^9 es metoxi (la amida 'Weinreb') por tratamiento con una diversidad de compuestos V^2Met donde Met es un metal, preferiblemente magnesio o litio, para producir los compuestos deseados de Fórmula XXV.

Los compuestos deseados de Fórmula XXVI donde R^1, R^2, R^4, R^5, R^6, R^7, R^8 y R^9 (que están dentro del alcance de esta invención) son como se han descrito

anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXIV por reducción con una fuente hidruro, preferiblemente borohidruro sódico, en presencia de un ácido tal como ácido trifluoroacético en un disolvente inerte a la reacción (preferiblemente tetrahidrofurano) a una temperatura comprendida entre 0ºC y 100ºC durante un periodo de tiempo comprendido entre 1 y 20 horas (preferiblemente 12 horas). Cuando R^8 y/o R^9 es H, la amina puede acilarse usando técnicas convencionales de acoplamiento de amida conocidas por los especialistas en la técnica tales como las descritas en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995, para producir otros compuestos de Fórmula XXVI.

Una preparación alternativa de los compuestos deseados de Fórmula XXVI donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y R^8 y R^9 son H implica la reducción de los correspondientes compuestos de Fórmula XXII usando procedimientos conocidos por los especialistas en la técnica, tales como los descritos en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995., por ejemplo, usando un complejo borano-tetrahidrofurano en un disolvente inerte a la reacción. Estas aminas primarias pueden transformarse posteriormente en amidas como se ha descrito anteriormente para producir otros compuestos dentro del alcance de la presente invención.

Los compuestos deseados de Fórmula XXVII donde R^1, R^2, R^4, R^5, R^6, R^7 y V^2 son como se han descrito anteriormente y X^1 es OH, F o H pueden prepararse a partir de los correspondientes compuestos de Fórmula XXV por tratamiento con un agente reductor tal como borohidruro sódico en un disolvente polar tal como metanol o etanol a una temperatura de aproximadamente 0ºC a aproximadamente 100ºC durante 1 a 10 horas (preferiblemente 1 hora) para producir compuestos de Fórmula XXVII en los que

X^1 es OH.

Los compuestos de Fórmula XXVII cuando X^1=N pueden prepararse con el alcohol correspondiente (X^1=OH) que se transforma en el mesilato y se sustituye con azida sódica. La azida se hidrogena a NH_2. Un especialista puede transformar NH_2 a NR^1H con condiciones convencionales de aminación reductora usando el correspondiente aldehído y agente reductor, tal como borohidruro sódico, ciano borohidruro sódico. NR^1H puede transformarse en NR^1R^2 usando las mismas condiciones de aminación reductora para producir NR^1R^2.

Además, cuando X^1 es NH_2, el alcohol correspondiente (X^1=OH) puede transformarse en el mesilato, sustituirse con un azida y reducirse con hidrógeno para producir un único diastereoisómero. Cuando X^1 es NHR^1 (R^1=Me), la correspondiente amina primaria NH_2 puede transformarse en NHR^1 por tratamiento con formiato de etilo a una temperatura comprendida entre 0°C y 100°C durante un periodo de tiempo comprendido entre 1-24 horas (preferiblemente 12 horas). La formamida resultante se añade directamente sin purificación adicional a un disolvente no polar (por ejemplo, benceno, tolueno, preferiblemente tolueno) y un agente reductor tal como un complejo borano sulfuro de metilo a una temperatura comprendida entre 0°C y 100°C durante un periodo comprendido entre 1-24 horas (preferiblemente 12 horas) para proporcionar el producto mono metilamina deseado. Cuando X^1 es NHR^1, la amina primaria correspondiente NHR^1 se puede transformar en NHR^1 en condiciones convencionales de aminación reductora por tratamiento con un aldehído R^1 en un disolvente polar tal como metanol o etanol en presencia de borohidruro sódico o cianoborohidruro sódico a una temperatura comprendida entre 0°C y 100°C durante un periodo comprendido entre 1-24 horas (preferiblemente 12 horas). Cuando X^1 es NR^1R^2, la correspondiente amina secundaria NHR^1 puede transformarse en NR^1R^2 por aminación reductora convencional

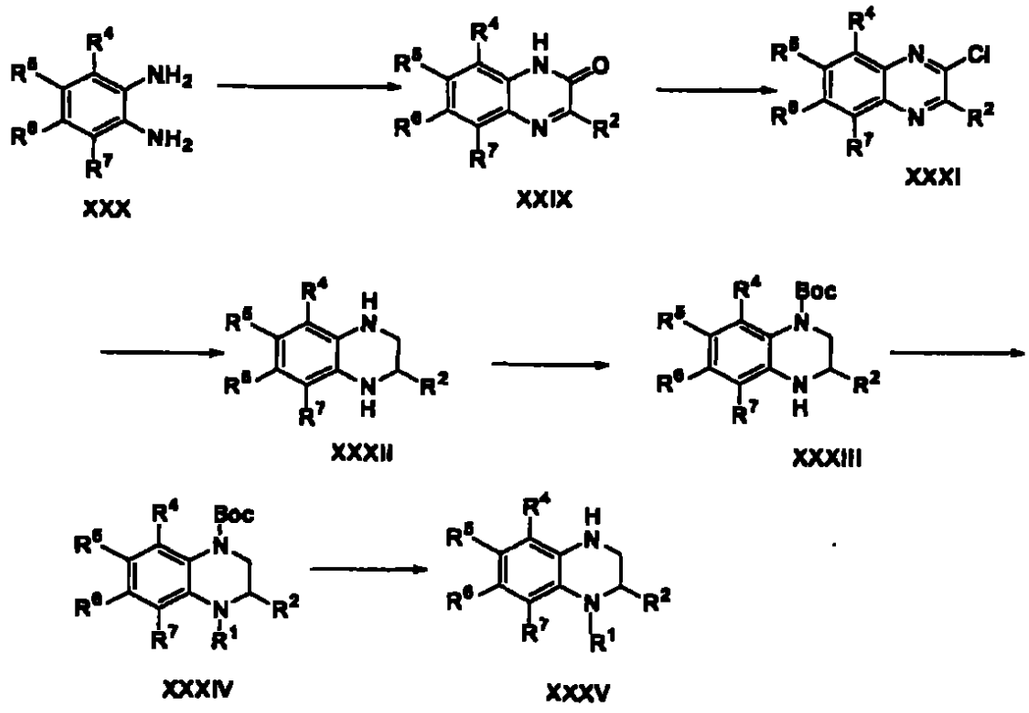
como se ha descrito anteriormente. El compuesto XXV también se puede transformar en NH_2, NHR^1 y NR^1R^2 con condiciones convencionales de aminación reductora con el correspondiente aldehído o cetona como se ha descrito anteriormente. Este procedimiento produce una mezcla de diastereómeros amina que se pueden separar por cromatografía en gel de sílice.

Éstos se pueden transformar en los correspondientes compuestos de Fórmula XXVII donde X^1 es F por tratamiento con un agente de fluoración, tal como trifluoruro de dietilaminoazufre (DAST) o trifluoruro de [bis(2-metoxietil)amino]azufre (Deoxyfluor) en un disolvente inerte a la reacción tal como diclorometano o 1,2-dicloroetano a una temperatura comprendida entre -78°C y aproximadamente 100°C (preferiblemente temperatura ambiente) durante un periodo comprendido entre 0,1 y 10 horas (preferiblemente 1 hora). Éstos se pueden transformar en los correspondientes compuestos de Fórmula XXVII en los que X^1 es H por reducción con una fuente hidruro adecuada tal como hidruro de diisobutil aluminio en un disolvente inerte a la reacción tal como tetrahidrofurano a una temperatura comprendida entre -78°C y aproximadamente 100°C, preferiblemente aproximadamente 0°C, durante un periodo comprendido entre 0,1 y 10 horas.

Los compuestos deseados de Fórmula XXVIII donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y V^2 es un grupo V o CH_2V donde V es como se ha descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXV por tratamiento con un agente de fluoración, tal como trifluoruro de dietilaminoazufre (DAST) o trifluoruro de [bis(2-metoxietil)amino]azufre (Deoxyfluor) en un disolvente inerte a la reacción tal como diclorometano o 1,2-dicloroetano a una temperatura comprendida entre -78°C y aproximadamente 100°C (preferiblemente temperatura ambiente) durante un periodo comprendido entre 0,1 y 24 horas

(preferiblemente 12 horas).

ESQUEMA 3



De acuerdo con el Esquema de Reacción 3, los compuestos deseados de Fórmula XXIX en los que J es nitrógeno, el enlace doble opcional está ausente y R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXX por reacción con un ácido alfa-cetocarboxílico R^2COCO_2H en un disolvente prótico, tal como etanol o metanol a alta temperatura. Estas temperaturas pueden conseguirse de forma práctica y segura usando un aparato de microondas familiar para el especialista, tal como un Emrys Optimizer (Personal Chemistry, Uppsala, Suecia) o un microondas Milestone (Milestone Laboratories, Sorisole, Italy). La mezcla de reacción resultante se concentra a sequedad y los compuestos de Fórmula XXIX pueden cristalizarse normalmente o

alternativamente purificarse por cromatografía ultrarrápida en gel de sílice.

Los compuestos deseados de Fórmula XXXI donde R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXIX por tratamiento con un agente de cloración tal como cloruro de fósforo (III), oxicloruro de fósforo (V), cloruro de tionilo o trifenifosfina/tetracloruro de carbono. Típicamente, los compuestos de Fórmula XXIX se disuelven en exceso de oxicloruro fosforoso y la mezcla se calienta a aproximadamente 100°C durante un periodo comprendido entre 12-18 horas. Después de enfriarse el exceso de oxicloruro de fósforo (V) se destila y el residuo se inactiva con precaución con $NaHCO_3$ saturado. La suspensión acuosa resultante se extrae con un disolvente orgánico apropiado, preferiblemente cloruro de metileno.

Los compuestos deseados de Fórmula XXXII donde R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXI por hidrogenación catalítica en presencia de catalizadores convencionales que conocen los especialistas en la técnica, por ejemplo, como los descritos en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. Típicamente, el compuesto se disuelve en un disolvente orgánico, preferiblemente un disolvente polar tal como ácido acético. Normalmente se añaden aditivos tales como acetato sódico para mejorar la velocidad de reacción. Se selecciona un catalizador apropiado, tal como paladio en carbono. La hidrogenación se realiza a presiones elevadas en un aparato apropiado, preferiblemente durante aproximadamente 6 horas. El catalizador se filtra para producir el compuesto de Fórmula XXXII, que se aísla típicamente después de la cromatografía en gel de sílice.

Los compuestos deseados de Fórmula XXXIII donde R^2, R^4, R^5, R^6 y R^7 son

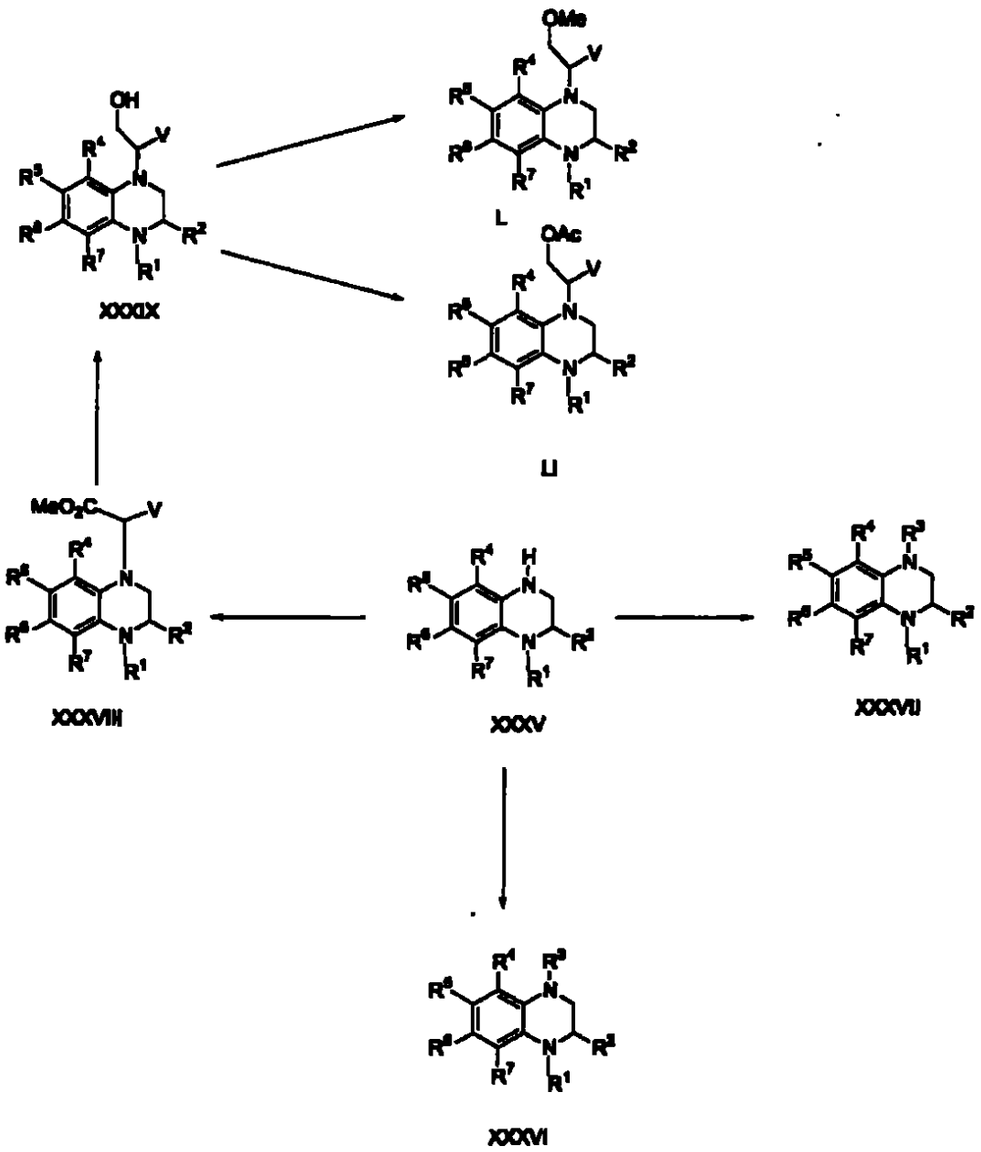
como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXII por reacción con boc-anhídrido como se describe en T.W. Greene y G.M. Wuts, Protective Groups in Organic Synthesis, Wiley Interscience, 1991. Típicamente, la reacción se realiza en un disolvente tal como cloruro de metileno a una temperatura comprendida entre -78°C y 0°C, típicamente -40°C. En general, en este procedimiento, se produce una funcionalización selectiva del nitrógeno menos impedido en los compuestos de Fórmula XXXII. Los compuestos de Fórmula XXXIII pueden purificarse, si es necesario, por cromatografía convencional en gel de sílice.

Los compuestos deseados de Fórmula XXXIV donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXIIII introduciendo el grupo R^1 acilo, carbamoílo, sulfinilo o sulfonilo. Esto puede realizarse por tratamiento con un reactivo apropiado, por ejemplo, cloroformiato de etilo o cloroformiato de isopropilo, en un disolvente inerte a la reacción tal como cloruro de metileno o cloroformo, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. A veces, la reacción se realiza con piridina como disolvente. El producto se aísla normalmente por tratamiento de extracción y cromatografía ultrarrápida en gel de sílice.

Los compuestos deseados de Fórmula XXXV donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXIV por tratamiento con un ácido como se describe en como se describe en T.W. Greene y G.M. Wuts, Protective Groups in Organic Synthesis, Wiley Interscience, 1991. En un procedimiento típico, el bis-carbamato se trata con ácido trifluoroacético a temperatura ambiente durante un periodo comprendido

entre 1-24 horas, típicamente 3 horas. Después de completarse, el ácido se retira por evaporación y el residuo se divide entre un disolvente orgánico, preferiblemente cloruro de metileno e hidrogenocarbonato sódico acuoso. La evaporación del disolvente orgánico produce los compuestos deseados de Fórmula XXXV.

ESQUEMA 4



De acuerdo con el Esquema de Reacción 4, los compuestos deseados en los que J es nitrógeno, el enlace doble opcional está ausente, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y R^3 es como se ha descrito anteriormente donde el carbono de unión está sustituido con oxo (representado como compuestos de Fórmula XXXVI) pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXV por reacción con un cloruro ácido, en un disolvente tal como cloruro de metileno o cloroformo, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. Después de completar la reacción, la mezcla se lava con ácido acuoso y salmuera para producir compuestos de Fórmula XXXVI después de cromatografía en gel de sílice. Si se desea, el cloruro ácido puede generarse *in situ*, con el correspondiente ácido carboxílico y trifenilfosfina junto con agentes tales como tetracloruro de carbono, hexacloroetano o tricloroacetonitrilo. Este último procedimiento puede realizarse con trifenilfosfina unida a resina lo que le hace utilizable para química automatizada. La filtración de la resina seguida de evaporación y purificación en gel de sílice produce el compuesto pedido de Fórmula XXXVI.

Los compuestos deseados de Fórmula XXXVII donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y R^3 es como se ha descrito anteriormente, donde el grupo V está unido al carbono de unión, pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXV por alquilación con los bromuros de alquilo apropiados. Estas alquilaciones se realizan típicamente en un disolvente polar tal como dimetilformamida, dimetilsulfóxido, N-metilpirrolidona, etc. en presencia de una base (por ejemplo, carbonato de potasio, trietilamina, piridina, 4-dimetilaminopiridina, lutidina) a una temperatura comprendida entre 25°C y 200°C, típicamente 150°C.

Debido a la no reactividad de las quinoxalinas, el calentamiento en el microondas a una temperatura apropiada es particularmente adecuado para este procedimiento. Las alquilaciones pueden realizarse con una diversidad de bromuros de alquilo, tale como bromuros de arilmetilo o bromuros de arilmetilo alfa-sustituidos. El uso de equipamiento microondas adecuado tal como Emrys Optimizer (Personal Chemistry, Uppsala, Suecia) o microondas Milestone (Milestone Laboratories, Sorisole, Italia) facilita estas reacciones.

Los compuestos deseados de Fórmula XXXVIII donde R^1, R^2, R^4, R^5, R^6, R^7 y V son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos alfa-bromoéster $VCHBrCO_2Me$. Estas alquilaciones se realizan típicamente en un disolvente polar tal como dimetilformamida, dimetilsulfóxido, N-metilpirrolidona, etc. en presencia de una base (por ejemplo, carbonato de potasio, trietilamina, piridina, 4-dimetilamina, lutidina) a una temperatura comprendida entre 25°C y 200°C, típicamente 150°C. Debido a la no reactividad de las quinoxalinas, el calentamiento en el microondas a una temperatura apropiada es particularmente adecuado para este procedimiento. El uso de equipamiento microondas adecuado tal como Emrys Optimizer (Personal Chemistry, Uppsala, Suecia) o microondas Milestone (Milestone Laboratories, Sorisole, Italia) facilita estas reacciones.

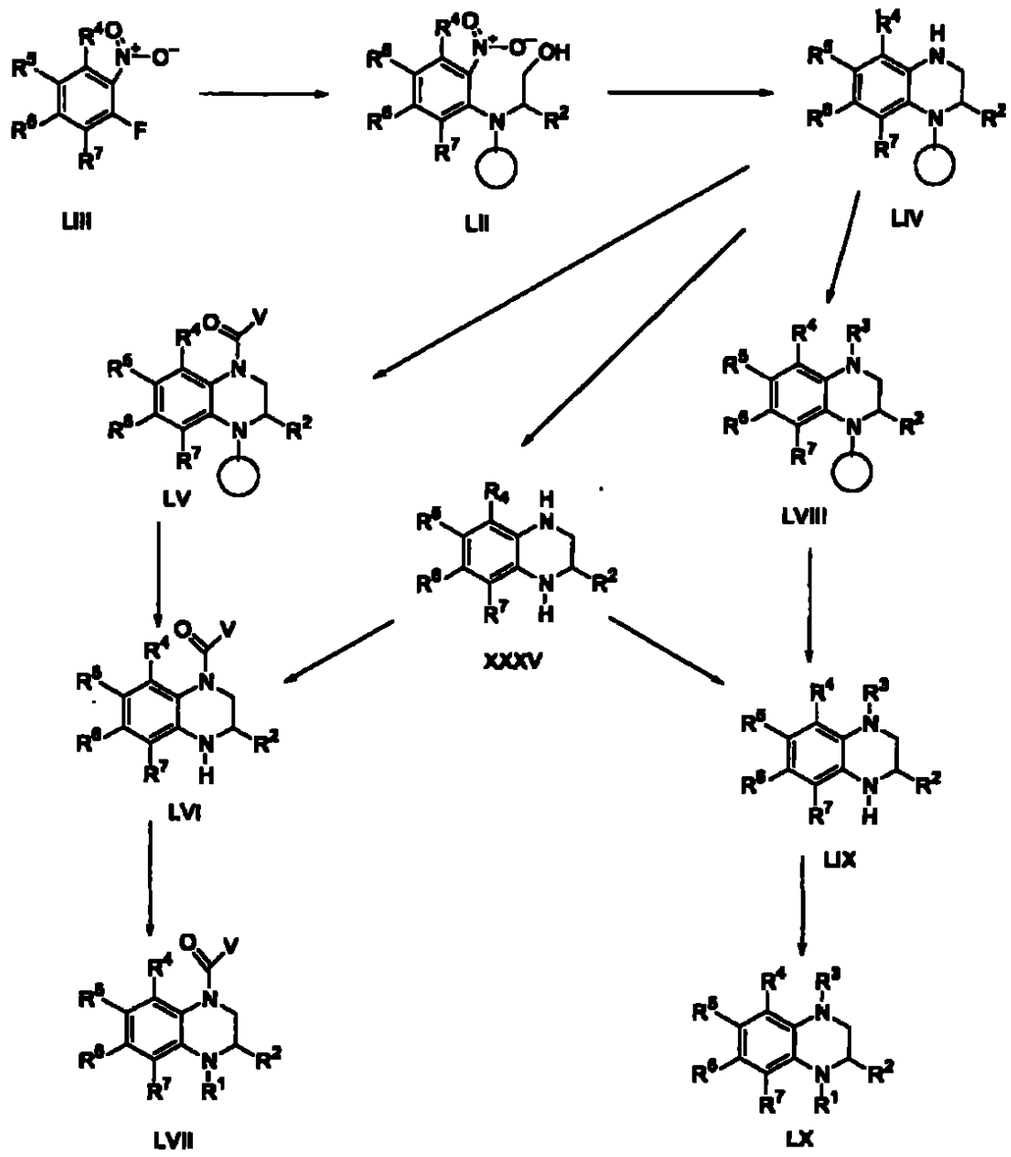
Los compuestos deseados de Fórmula XXXIX donde R^1, R^2, R^4, R^5, R^6, R^7 y V son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXVIII por reducción de la funcionalidad éster usando reactivos y condiciones que conocen los especialistas en la técnica. Por ejemplo, los compuestos de Fórmula XXXVIII pueden tratarse con hidruro de aluminio y litio en disolventes etéreos anhidros tales como tetrahidrofurano y éter a temperaturas comprendidas en el intervalo entre -78°C y 0°C. Típicamente, el tratamiento de la

mezcla de reacción con sulfato sódico hexahidrato o gel de sílice/cloroformo y la retirada de los sólidos por filtración da un producto en bruto a partir del cual se aíslan típicamente los compuestos de Fórmula XXXIX por cromatografía en gel de sílice.

Los compuestos deseados de Fórmula L donde R^1, R^2, R^4, R^5, R^6, R^7 y V son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXIX usando un agente de alquilación apropiado, tal como yoduro o bromuro de alquilo y una base, tal como hidruro sódico, en un disolvente inerte a la reacción tal como tetrahidrofurano o dimetilformamida para obtener los compuestos deseados de Fórmula L.

Los compuestos deseados de Fórmula LI donde R^1, R^2, R^4, R^5, R^6, R^7 y V son como se han descrito anteriormente y Ac es un grupo acilo (que están dentro del alcance de la presente invención) pueden prepararse a partir de los correspondientes compuestos de Fórmula XXXIX usando un cloruro de acilo adecuado y una base tal como piridina, trietilamina o 4-dimetilaminopiridina en un disolvente anhidro tal como diclorometano. Dependiendo de la reactividad del cloruro de acilo, se puede usar una base, tal como piridina, como disolvente. Los productos pueden aislarse normalmente concentrando la mezcla de reacción y purificando el producto por cromatografía en gel de sílice.

ESQUEMA 5



El Esquema de Reacción 5 describe la preparación de otros compuestos, en los que J en nitrógeno y el enlace doble opcional está ausente (es decir, quinoxalinas), usando química de fase sólida similar a la descrita en V. Krchnak *et al.*, *Tetrahedron*

Lett. 42, 2443-2446 (2001) y que ofrece ciertas ventajas. Esta química también puede realizarse en fase de solución sustituyendo la resina con un grupo arilmetilo rico en electrones, tal como 4-metoxibencilo o 2,4-dimetoxibencilo y usándolo como un grupo protector y escindiendo en condiciones apropiadas como las descritas en T.W. Greene y G.M. Wuts, Protective Groups in Organic Synthesis, Wiley Interscience, 1991. En particular, este esquema proporciona un procedimiento para preparar quinoxalinas quirales con aminoalcoholes quirales, que se preparan fácilmente con aminoácidos quirales ampliamente disponibles usando procedimientos y reactivos que conocen los especialistas en la técnica.

Los compuestos deseados de Fórmula LII unidos a resina donde R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes aminoalcoholes $R^2CH(CH_2OH)NH_2$ que se unen primero a una resina por el procedimiento descrito en V. Krchnak *et al.*, *Tetrahedron Lett. 42*, 2443-2446 (2001). Después, esto se trata con los correspondientes compuestos de Fórmula LIII típicamente en un disolvente polar tal como dimetilsulfóxido, dimetilformamida, N-metilpirrolidona o dimetilacetamina que permite a la resina basada en poliestireno hincharse como conocen los especialistas en la técnica. La reacción se realiza durante un periodo comprendido entre 12-36 horas y después, la resina se lava para aislar los compuestos deseados de Fórmula LII unidos a la resina.

Los compuestos deseados de Fórmula LIV unidos a resina donde R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes alcoholes unidos a resina de compuestos de Fórmula LII activando la funcionalidad alcohol de una forma familiar para el especialista en la técnica. Esto implica la conversión del alcohol a un sulfonato (tal como un metanosulfonato o toluenosulfonato), haluro (tal como cloruro o bromuro) o un acetato. Preferiblemente, la

reacción se realiza por tratamiento de los compuestos de Fórmula LII unidos a resina con cloruro de metanosulfonilo en presencia de una base tal como piridina, 4-dimetilaminopiridina o esponja protónica en disolventes tales como diclorometano o dicloroetano en cuyo caso la reacción se realiza típicamente durante un periodo comprendido entre 1-5 horas. El sulfonato unido a resina resultante se lava para retirar todos los reactivos y el grupo nitro se puede reducir con una diversidad de agentes reductores que conocen los especialistas en la técnica, por ejemplo los descritos en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. Por ejemplo, se puede usar cloruro de estaño (II) en un disolvente polar tal como N-metilpirrolidona o dimetilformamida, que pueden hinchar una resina basada en poliestireno. La reacción se realiza típicamente durante un periodo comprendido entre 1-5 horas, los reactivos se eliminan por lavado y la amina primaria resultante experimenta un cierre del anillo intramolecular para producir los compuestos de Fórmula LIV unidos a la resina. Si se usa un grupo activador distinto de un metanosulfonato como se ha descrito anteriormente, los tiempos de reacción para el cierre del anillo pueden ser más largos, como conocen los especialistas en la técnica.

Los compuestos deseados de Fórmula LV unidos a resina donde R^2, R^4, R^5, R^6, R^7 y V son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula LIV, por reacción con un cloruro ácido VOCl en un disolvente tal como cloruro de metileno o cloroformo, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. El compuesto de Fórmula LV unido a resina se filtra posteriormente y se lava repetidamente con disolventes tales como diclorometano, metanol y agua para retirar el

exceso de reactivos.

Los compuestos deseados de Fórmula LVI donde R^2, R^4, R^5, R^6,R^7 y V son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula LV unidos a resina, por tratamiento con un ácido fuerte conocido por los especialistas en la técnica, tal como ácido trifluoroacético o ácido fluorhídrico, opcionalmente en un disolvente inerte a la reacción tal como diclorometano o dicloroetano. Típicamente, los compuestos deseados de Fórmula LVI pueden aislarse por filtración y se pueden lavar para retirar la resina con un disolvente orgánico apropiado tal como diclorometano, dicloroetano o tetrahidrofurano. Si es necesario, los compuestos de Fórmula LVI pueden purificarse adicionalmente por cromatografía en gel de sílice usando condiciones convencionales.

Los compuestos deseados de Fórmula LVII donde R^1, R^2, R^4, R^5, R^6, R^7 y V son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula LVI por tratamiento con un reactivo apropiado, por ejemplo, clorformiato de etilo o cloroformiato de isopropilo, en un disolvente inerte a la reacción tal como cloruro de metileno o cloroformo, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. A veces, la reacción se realiza con piridina como disolvente. En el caso particular en el que R^1 es carbamato o urea, el producto puede obtenerse tratando compuestos de Fórmula LVI con fosgeno en tolueno, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, seguido de tratamiento, respectivamente, con un alcohol o una amina para producir el carbamato o urea deseado de Fórmula LVII. El producto se aísla

normalmente por tratamiento extractivo convencional y cromatografía ultrarrápida en gel de sílice.

Los compuestos deseados unidos a resina de Fórmula LVIII donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y R^3 es como se ha descrito anteriormente, donde el grupo V está unido al carbono de unión, pueden prepararse a partir de los correspondientes compuestos unidos a resina de Fórmula LIV por alquilación con los bromuros o yoduros de alquilo apropiados. Estas alquilaciones se realizan típicamente en un disolvente polar tal como dimetilformamida, dimetilsulfóxido, N-metilpirrolidona, etc. en presencia de una base (por ejemplo, carbonato de potasio, trietilamina, piridina, 4-dimetilaminopiridina, lutidina). Los disolventes usados en esta reacción permiten a una resina de poliestireno hincharse de forma familiar para un especialista en la técnica. Estas reacciones se realizan normalmente a una temperatura comprendida entre temperatura ambiente y aproximadamente 150°C Debido a la no reactividad de las quinoxalinas, se prefiere particularmente calentar en un horno microondas a una temperatura apropiada. Las alquilaciones pueden realizarse con una diversidad de bromuros de alquilo, tales como bromuros de arilmetilo o bromuros de arilmetilo alfa-sustituidos. Las reacciones de alquilación producen típicamente mejores rendimientos si los bromuros están sustituidos con un grupo alfa que retira electrones (tal como en la preparación de los compuestos de Fórmula XXXVIII del Esquema 4).

Los compuestos de quinoxalina de Fórmula LIX donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos unidos a resina de Fórmula LVIII, por tratamiento con ácidos fuerte conocidos por los especialistas, tal como ácido trifluoroacético o ácido fluorhídrico, con o sin disolventes adicionales (tales como diclorometano o

dicloroetano). Típicamente, los compuestos deseados de Fórmula LIX pueden aislarse por filtración y se pueden lavar para retirar la resina con un disolvente orgánico apropiado tal como diclorometano, dicloroetano o tetrahidrofurano. La evaporación del disolvente produce típicamente los compuestos de Fórmula LIX limpios. Si es necesario, los compuestos aislados pueden purificarse adicionalmente por cromatografía en gel de sílice usando condiciones convencionales.

Los compuestos deseados de Fórmula LX donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula LIX, por tratamiento con un disolvente con agente de acilación/sulfonación, por ejemplo cloroformiato de etilo o de isopropilo en un disolvente inerte a la reacción tal como cloruro de metileno o cloroformo, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. A veces, la reacción se realiza con piridina como disolvente. En el caso particular en el que R^1 es carbamato o urea, el producto puede obtenerse tratando compuestos de Fórmula LX con fosgeno en tolueno, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0°C y 60°C, seguido de tratamiento, respectivamente, con un alcohol o una amina para producir el carbamato o urea deseado de Fórmula LX. El producto se aísla normalmente por tratamiento de extracción convencional y cromatografía ultrarrápida en gel de sílice.

Una preparación alternativa de los compuestos deseados de Fórmula LVI donde R^2, R^4, R^5, R^6, R^7 y V son como se han descrito anteriormente puede conseguirse a partir de los correspondientes compuestos de Fórmula XXXV por reacción con un

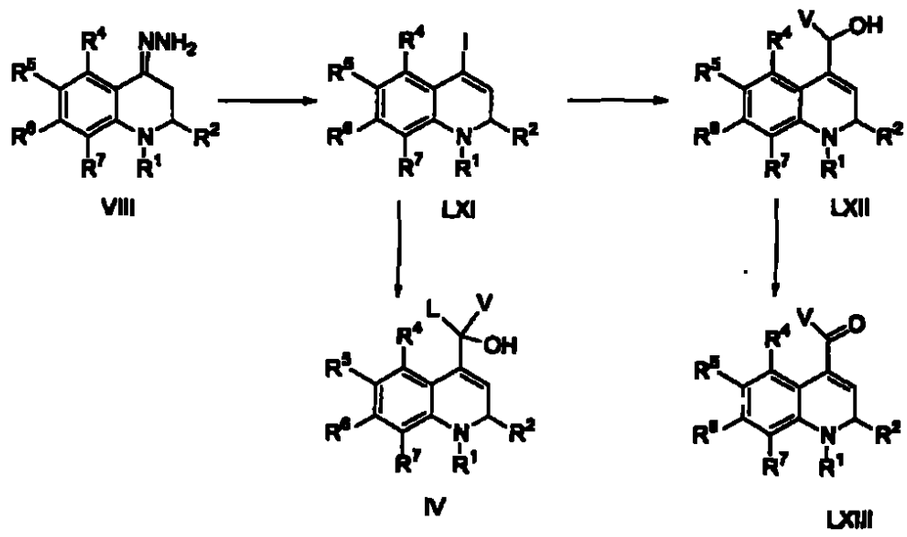
agente de acilación tal como cloruro ácido VOCl, en un disolvente inerte a la reacción tal como cloruro de metileno o cloroformo, conteniendo opcionalmente una base tal como piridina, diisopropiletilamina, 4-dimetilaminopiridina o 2,6-di-terc-butil-4-metilpiridina a una temperatura comprendida entre 0ºC y 60ºC, típicamente temperatura ambiente, durante un periodo comprendido entre 1 y 24 horas. Típicamente, en estas condiciones, cuando R^2 es distinto de hidrógeno, el átomo de nitrógeno menos impedido de la quinoxalina experimenta preferiblemente acilación para dar los compuestos deseados de Fórmula LVI. Los compuestos deseados de Fórmula LVII donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y R^3 es como se ha descrito anteriormente, donde el grupo V está unido al carbono de unión, pueden conseguirse a partir de los correspondientes compuestos de Fórmula LVI por alquilación o acilación, usando procedimientos como los descritos anteriormente.

Una preparación alternativa de los compuestos deseados de Fórmula LIX donde R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente y R^3 es como se ha descrito anteriormente, donde el grupo V está unido al carbono de unión, pueden conseguirse a partir de los correspondientes compuestos de Fórmula XXXV, con los compuestos de Fórmula LIX, por alquilación con los bromuros o yoduros de alquilo apropiados. Estas alquilaciones se realizan típicamente en un disolvente polar tal como dimetilformamida, dimetilsulfóxido, N-metilpirrolidona, etc. en presencia de una base (por ejemplo, carbonato de potasio, trietilamina, piridina, 4-dimetilaminopiridina, lutidina). Estas reacciones se realizan normalmente a una temperatura comprendida entre temperatura ambiente y aproximadamente 150ºC Debido a la no reactividad de las quinoxalinas, se prefiere particularmente calentar en un horno microondas a una temperatura apropiada. Las alquilaciones pueden realizarse con una diversidad de bromuros de alquilo, tales como bromuros de arilmetilo o bromuros de arilmetilo alfa-sustituidos. Típicamente, en

estas condiciones, cuando R^2 es distinto de hidrógeno, el átomo de nitrógeno menos impedido de la quinoxalina experimenta preferiblemente alquilación para dar los compuestos deseados de Fórmula LIX.

Los compuestos deseados de Fórmula XXXV donde R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos unidos a resina de Fórmula LIV por tratamiento con ácidos fuertes conocidos por los especialistas en la técnica, tales como ácido trifluoroacético o ácido fluorhídrico, opcionalmente en un disolvente inerte a la reacción tal como diclorometano o dicloroetano.

ESQUEMA 6



De acuerdo con el Esquema de Reacción 6, los compuestos deseados en los que J es carbono, el enlace doble opcional está presente, R^3 es un grupo COV y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente (representados como compuestos de Fórmula LXIII) pueden prepararse a partir de los correspondientes compuestos de Fórmula LXII por oxidación del alcohol. Esto puede realizarse con una

diversidad de procedimientos que conocen los especialistas en la técnica, por ejemplo, los descritos en L.A. Paquette (Ed), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Chichester, England, 1995. Por ejemplo, los compuestos de Fórmula LXII pueden tratarse con óxido de manganeso (IV) activado en un disolvente inerte a la reacción adecuado tal como tetrahidrofurano, éter dietílico o diclorometano a una temperatura comprendida entre 0°C y 25°C, típicamente temperatura ambiente, para proporcionar el producto deseado de Fórmula LXIII.

Los compuestos deseados de Fórmula LXII donde V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse en forma de una mezcla de diastereoisómeros a partir de los correspondientes compuestos de Fórmula LXI por tratamiento con un agente de transmetalación adecuado tal como un compuesto de alquillitio, tal como n-butillitio o s-butillitio, o un haluro de alquilmagnesio tal como cloruro de isopropilmagnesio en un disolvente inerte a la reacción adecuado tal como tetrahidrofurano o éter dietílico a una temperatura comprendida entre -120°C y 0°C, típicamente -78°C, para proporcionar una especie de vinillitio que después reacciona con el aldehído apropiado de fórmula VCHO a una temperatura comprendida ente -120°C y 0°C, típicamente -78°C a -23°C para proporcionar el producto deseado de Fórmula LXII. En algunos casos, es conveniente añadir el agente de transmetalación a una mezcla del aldehído y del yoduro.

Los compuestos deseados de Fórmula LXI donde R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente pueden prepararse a partir de los correspondientes compuestos de Fórmula VIII (preparados como se ha descrito en el Esquema I) usando el procedimiento general descrito por D.H.R. Barton et al. (Tetrahedron Letters **1983** *24*, 1605) en el que la hidrazona reacciona con yodo en presencia de un base impedida adecuada tal como 1,1,3,3-tetrametilguanidina en un disolvente inerte a la reacción

adecuado tal como tetrahidrofurano a una temperatura comprendida entre 25°C y 100°C, típicamente 25°C a 85°C, retirando el disolvente en el curso de la reacción, para proporcionar el producto deseado de Fórmula LXI.

Una preparación alternativa de los compuestos deseados de Fórmula IV donde L es un grupo alcoxicarbonilo (C_1-C_6) y V, R^1, R^2, R^4, R^5, R^6 y R^7 son como se han descrito anteriormente puede realizarse de una forma similar a la descrita para la preparación de los compuestos de Fórmula LXII a partir de los correspondientes compuestos de Fórmula LXI por tratamiento con un agente de transmetalación adecuado tal como un compuesto de alquillitio, tal como n-butillitio o s-butillitio, o un haluro de alquilmagnesio tal como cloruro de isopropilmagnesio en un disolvente inerte a la reacción adecuado tal como tetrahidrofurano o éter dietílico a una temperatura comprendida entre -120°C y 0°C, típicamente -78°C, para proporcionar una especie de vinillitio que después reacciona con la cetona apropiada de fórmula VCOL a una temperatura comprendida ente -120°C y 0°C, típicamente -78°C a -23°C para proporcionar el producto deseado de Fórmula IV. En algunos casos, es conveniente añadir el agente de transmetalación a una mezcla de la cetona y del yoduro.

Como nota inicial, en la preparación de compuestos, se aprecia que algunos de los procedimientos de preparación útiles para la preparación de los compuestos descritos en este documento pueden requerir la protección de una funcionalidad remota (por ejemplo, amina primaria, amina secundaria, carboxilo en los intermedios). La necesidad de tal protección variará dependiendo de la naturaleza de la funcionalidad remota y de las condiciones de los procedimientos de preparación. El especialista en la técnica determina fácilmente la necesidad de tal protección. El uso de tales procedimientos de protección/desprotección también está incluido en la técnica. Para una descripción general de grupos protectores y de su uso, véase T.W. Greene y G.M.

Wuts, Protective Groups in Organic Synthesis, Wiley Interscience, 1991.

Por ejemplo, en los esquemas de reacción, ciertos compuestos contienen funcionalidades de amina primaria o de ácido carboxílico que pueden interferir con las reacciones en otros sitios de la molécula si se dejan desprotegidas. En consecuencia, tales funcionalidades pueden protegerse con un grupo protector adecuado que puede retirarse en una etapa posterior. Los grupos protectores adecuados para la protección de aminas y ácido carboxílico incluyen aquellos grupos protectores usados habitualmente en la síntesis de péptidos (tales como N-t-butoxicarbonilo, benciloxicarbonilo y 9-fluorenilmetilenoxicarbonilo para aminas y alquilo inferior o ésteres de bencilo para ácidos carboxílicos) que generalmente no son reactivos químicamente en las condiciones de reacción descritas y pueden eliminarse típicamente sin alterar químicamente otra funcionalidad del compuesto.

Los profármacos de los compuestos de la presente invención pueden prepararse de acuerdo con procedimientos conocidos por los especialistas. Algunos ejemplos de procesos se describen a continuación.

Los profármacos de esta invención en los que un grupo carboxilo de un ácido carboxílico del compuesto se reemplaza con un éster pueden prepararse combinando el ácido carboxílico con un haluro de alquilo apropiado en presencia de una base tal como carbonato de potasio en un disolvente inerte tal como dimetilformamida a una temperatura comprendida entre aproximadamente 0 y 100°C durante un periodo comprendido entre aproximadamente 1 y aproximadamente 24 horas. Alternativamente, el ácido se combina con un alcohol apropiado como disolvente en presencia de una cantidad catalítica de ácido tal como ácido sulfúrico concentrado a una temperatura comprendida entre aproximadamente 20 y 100°C, preferiblemente a reflujo, durante un periodo comprendido entre aproximadamente 1 hora y aproximadamente 24 horas. Otro

procedimiento es la reacción del ácido con una cantidad estequiométrica del alcohol en presencia de una cantidad catalítica de ácido en un disolvente inerte tal como tolueno o tetrahidrofurano, con retirada concomitantee del agua por medios físicos (por ejemplo, trampa Dean-Stark) o químicos (por ejemplo, tamices moleculares).

Los profármacos de esta invención en los que una función alcohol se ha derivatizado en forma de éter pueden prepararse combinando el alcohol con el bromuro o yoduro apropiado en presencia de una base tal como carbonato de potasio en un disolvente inerte tal como dimetilformamida a una temperatura comprendida entre aproximadamente 0 y 100°C durante un periodo comprendido entre 1 hora y aproximadamente 24 horas. Los éteres de alcanoilaminometilo pueden obtenerse por reacción del alcohol con un bis-(alcanoilamino)metano en presencia de una cantidad catalítica de ácido en un disolvente inerte tal como tetrahidrofurano, de acuerdo con un procedimiento descrito en la Patente de Estados Unidos Nº 4.997.984. Alternativamente, estos compuestos pueden prepararse con los procedimientos descritos por Hoffmann et al. en J. Org. Chem. 1994, 59, 3530.

Los glicósidos se preparan por reacción del alcohol y un carbohidrato en un disolvente inerte tal como tolueno en presencia de un ácido. Típicamente, el agua formada en la reacción se retira mientras se forma como se ha descrito anteriormente. Un procedimiento alternativo es la reacción del alcohol con un haluro de glicosilo adecuadamente protegido en presencia de una base seguido de desprotección.

Los N-(1-hidroxialquil)amiduros, N-(1-hidroxi-1-(alcoxicarbonil)metil)amiduros pueden prepararse por reacción del amiduro precursor con el aldehído apropiado en condiciones neutras o básicas (por ejemplo, etóxido sódico en etanol) a temperaturas comprendidas entre 25 y 70°C. Los derivados de N-alcoximetilo o N-1-(alcoxi)alquilo pueden obtenerse por reacción del compuesto N-no sustituido con el haluro de alquilo

necesario en presencia de una base en un disolvente inerte.

Los compuestos de esta invención también pueden usarse junto con otros agentes farmacéuticos (por ejemplo, agentes que disminuyen el colesterol-LDL, agentes que disminuyen los niveles de triglicéridos) para el tratamiento de las enfermedades/afecciones descritas en este documento. Por ejemplo, pueden usarse en combinación con un inhibidor de la HMG CoA reductasa, un inhibidor de la síntesis de colesterol, un inhibidor de la absorción de colesterol, un inhibidor de la secreción de MTP/Apo B, un modulador de PPAR y otros agentes que disminuyen los niveles de colesterol tales como un fibrato, niacina, una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT y un secuestrador de ácidos biliares. Otros agentes farmacéuticos también incluirán los siguientes: un inhibidor de recaptación de ácidos biliares, un inhibidor del transporte de ácido biliar ileal, un inhibidor de la ACC, un antihipertensivo (tal como NORVASC®), un modulador selectivo del receptor de estrógenos, un modulador selectivo del receptor de andrógenos, un antibiótico, un antidiabético (tal como metformin, un activador de PPARγ, una sulfonilurea, insulina, un inhibidor de la aldosa reductasa (ARI) y un inhibidor de la sorbitol deshidrogenasa (SDI)) y aspirina (ácido acetilsalicílico). Está disponible una forma de niacina de liberación lenta y se conoce como Niaspan. La niacina también puede combinarse con otros agentes terapéuticos tales como estatinas, es decir, lovastatina, que es un inhibidor de la HMG CoA reductasa y se describe adicionalmente más adelante. Esta terapia de combinación se conoce como ADVICOR® (Kos Pharmaceuticals Inc.). En la terapia de combinación, tanto los compuestos de esta invención como las demás terapias con fármacos se adminsitran a mamíferos (por ejemplo, seres humanos, hombres o mujeres) por procedimientos convencionales.

Se puede usar cualquier inhibidor de la HMG CoA reductasa en el aspecto de

combinación de esta invención. La expresión inhibidor de la HMG CoA reductasa se refiere a compuestos que inhiben la bioconversión de la hidroximetilglutaril-coenzima A en ácido mevalónico catalizada por la enzima HMG CoA reductasa. Los especialistas en la técnica determinan fácilmente tal inhibición de acuerdo con ensayos convencionales (por ejemplo, Meth. Enzymol. 1981; 71:455-509 y las referencias citadas en este documento). Más adelante se describen y hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros inhibidores de la HMG CoA reductasa. La Patente de Estados Unidos Nº 4.231.938 (cuya descripción se incorpora en este documento como referencia) describe ciertos compuestos aislados después de cultivar un microorganismo que pertenece al género *Aspergillus*, tal como lovastatina. Además, la Patente de Estados Unidos Nº 4.444.784 (cuya descripción se incorpora en este documento como referencia) describe derivados sintéticos de los compuestos mencionados anteriormente, tales como simvastatina. Además, la Patente de Estados Unidos Nº 4.739.073 (cuya descripción se incorpora en este documento como referencia) describe cierto indoles sustituidos, tales como fluvastatina. Además, la Patente de Estados Unidos Nº 4.343.227 (cuya descripción se incorpora en este documento como referencia) describe derivados de ML-236B, tales como pravastatina. Además, el documento EP-491226A (cuya descripción se incorpora en este documento como referencia) describe ciertos ácidos piridilhidroxiheptenoicos, tales como cerivastatina. Además, la Patente de Estados Unidos Nº 5.273.995 (cuya descripción se incorpora en este documento como referencia) describe ciertas 6-[2-(sustituido pirrol-1-il)alquil]piran-2-onas tales como atorvastatina y cualquier forma farmacéuticamente aceptable de las mismas (es decir, LIPITOR®). Otros inhibidores de la HMG-CoA reductasa incluyen rosuvastatina y pitavastatina.

En el aspecto de combinación de esta invención puede usarse cualquier

modulador de PPAR. La expresión modulador de PPAR se refiere a compuestos que modulan la actividad del receptor activador del proliferador de peroxisomas (PPAR) en mamíferos, particularmente en seres humanos. Los especialistas en la técnica determinan fácilmente tal modulación de acuerdo con ensayos convencionales conocidos en la bibliografía. Se cree que tales compuestos, al modular el receptor PPAR, regulan la transcripción de genes clave implicados en el metabolismo de lípidos y de glucosa tales como los implicados en la oxidación de ácidos grasos y también los implicados en la unión de lipoproteínas de alta densidad (HDL) (por ejemplo, la transcripción del gen de la apolipoproteína Al), reduciendo, por consiguiente, toda la grasa corporal y aumentando el colesterol HDL. Debido a su actividad, estos compuestos también reducen los niveles en plasma de triglicéridos, colesterol VLDL, colesterol LDL y sus componentes asociados tales como apolipoproteína B en mamíferos, particularmente seres humanos, al igual que aumentan el colesterol HDL y la apolipoproteína Al. Por tanto, estos compuestos son útiles para el tratamiento y corrección de diversas dislipidemias que se observa que se asocian con el desarrollo y la incidencia de la aterosclerosis y la enfermedad cardiovascular, incluyendo hipoalfalipoproteinemia e hipertrigliceridemia. Más adelante se describen y se hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros. Las Publicaciones Internacionales N° WO 02/064549 y 02/064130 y la Solicitud de Patente de Estados Unidos 10/720942, presentada el 24 de Noviembre de 2003 (cuyas descripciones se incorporan en este documento como referencia) describen ciertos compuestos que son activadores de PPARα.

En el aspecto de combinación de esta invención puede usarse cualquier inhibidor de la secreción de MTP/Apo B (proteína de transferencia de triglicéridos microsomal y/o apolipoproteína B). La expresión inhibidor de la secreción de MTP/Apo B se refiere

a compuestos que inhiben la secreción de triglicéridos, éster de colesterol y fosfolípidos. Tal inhibición se determina fácilmente por parte de los especialistas en la técnica de acuerdo con ensayos convencionales (por ejemplo, Wetterau, J.R. 1992; Science 258:999). Más adelante se describen y se hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros inhibidores de la secreción de MTP/Apo B, incluyendo imputapride (Bayer) y otros compuestos tales como aquellos descritos en los documentos WO 96/40640 y WO 98/23593 (dos publicaciones ilustrativas).

Por ejemplo, los siguientes inhibidores de la secreción de MTP/Apo B son particularmente útiles:

[2-(1H-[1,2,4]triazol-3-ilmetil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida del ácido 4'-trifluorometil-bifenil-2-carboxílico;

[2-(2-acetilamino-etil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida del ácido 4'-trifluorometil-bifenil-2-carboxílico;

Éster metílico del ácido (2-{6-[(4'-trifluorometil-bifenil-2-carbonil)-amino]-3,4-dihidro-1H-isoquinolin-2-il}-etil)-carbámico;

[2-(1H-imidazol-2-ilmetil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida del ácido 4'-trifluorometil-bifenil-2-carboxílico;

[2-(2,2-difenil-etil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida del ácido 4'-trifluorometil-bifenil-2-carboxílico;

[2-(2-etoxi-etil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida del ácido 4'-trifluorometil-bifenil-2-carboxílico.

En el aspecto de esta invención puede usarse cualquier inhibidor de la HMG-CoA sintasa. La expresión inhibidor de la HMG-CoA sintasa se refiere a compuestos que inhiben la biosíntesis de hidroximetilglutaril-coenzima A en acetil-coenzima A y

acetoacetil-coenzima A, catalizada por la enzima HMG-CoA sintasa. Los especialistas en la técnica determinan fácilmente tal inhibición de acuerdo con ensayos convencionales (por ejemplo, Meth Enzymol. 1975; 35:155-160: Meth. Enzymol. 1985; 110:19.26 y referencias citadas en estos documentos). Más adelante se describen y se hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros inhibidores de la HMG-CoA sintasa. La Patente de Estados Unidos Nº 5.120.729 (cuya descripción se incorpora en este documento como referencia) describe ciertos derivados de beta-lactama. La Patente de Estados Unidos Nº 5.064.856 (cuya descripción se incorpora en este documento como referencia) describe ciertos derivados de espiro-lactona preparados cultivando un microorganismo (MF5253). La Patente de Estados Unidos Nº 4.847.271 (cuya descripción se incorpora en este documento como referencia) describe ciertos compuestos de oxetano tales como derivados del ácido 11-(3-hidroximetil-4-oxo-2-oxetil)-3,5,7-trimetil-2,4-undeca-dienoico.

En el aspecto de combinación de esta invención puede usarse cualquier compuesto que reduzca la expresión del gen de la HMG-CoA reductasa. Estos agentes pueden ser inhibidores de la transcripción de la HMG-CoA reductasa que bloquean la transcripción de ADN o inhibidores de traducción que previenen o reducen la traducción ARNm que codifica para la HMG-CoA en proteína. Tales compuestos pueden afectar a la transcripción o traducción directamente, o pueden biotransformarse en compuestos que tienen las actividades mencionadas anteriormente mediante una o más enzimas en la cascada biosintética del colesterol o pueden conducir a la acumulación de un metabolito de isopreno que tiene las actividades mencionadas anteriormente. Tales compuestos pueden causar este efecto disminuyendo los niveles de SREBP (proteína de unión del receptor de esterol) inhibiendo la actividad de la proteasa

sitio-1 (S1P) o agonizando el receptor oxagenal o SCAP. Los especialistas en la técnica determinan fácilmente tal regulación de acuerdo con ensayos convencionales (Meth Enzymol. 1985; 110:9-19). Más adelante se describen y se hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros inhibidores de la expresión del gen de la HMG-CoA reductasa. La Patente de Estados Unidos Nº 5.041.432 (cuya descripción se incorpora en este documento como referencia) describe ciertos derivados de lanoesterol 15-sustituidos. Se describen otros esteroles oxigenados que suprimen la síntesis de la HMG-CoA reductasa en E.I. Mercer (Prog. Lip. Res. 1993:32-357-416).

En el aspecto de combinación de esta invención puede usarse cualquier inhibidor de la escualeno sintetasa. La expresión "inhibidor de escualeno sintetasa" se refiere a compuestos que inhiben la condensación de 2 moléculas de farnesilpirofosfato para formar escualeno, catalizada por la enzima escualeno sintetasa. Los especialistas en la técnica determinan fácilmente tal inhibición de acuerdo con ensayos convencionales (Meth Enzymol. 1969; 15: 393-454 y Meth. Enzymol. 1985; 110:359-373 y referencias contenidas en este documento). Más adelante se describen y se hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros inhibidores de la escualeno sintetasa. La Patente de Estados Unidos Nº 5.026.556 (cuya descripción se incorpora en este documento como referencia) describe productos de fermentación del microorganismo MF5465 (ATCC 74011) incluyendo ácido zaragózico. Se ha recopilado un resumen de otros inhibidores patentados de la escualeno sintetasa (Curr. Op. Ther. Patents (1993) 861-4).

En el aspecto de combinación de esta invención puede usarse cualquier inhibidor de la escualeno epoxidasa. La expresión inhibidor de la escualeno epoxidasa se refiere a compuestos que inhiben la bioconversión de escualeno y oxígeno molecular en

escualeno-2,3-epóxido, catalizada por la enzima escualeno epoxidasa. Los especialistas en la técnica determinan fácilmente tal inhibición de acuerdo con ensayos convencionales (Biochim. Biophys. Acta 1984; 794:466-471). Más adelante se describen y se hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros inhibidores de escualeno epoxidasa. Las Patente de Estados Unidos N° 5.011.859 y 5.064.864 (cuyas descripciones se incorporan en este documento como referencia) describen ciertos análogos fluoro de escualeno. La publicación EP 395.768 A (cuya descripción se incorpora como referencia) describe ciertos derivados de alilamina sustituidos. La publicación PCT WO 9312069 A (cuya descripción se incorpora como referencia) describe ciertos derivados de aminoalcohol. La Patente de Estados Unidos N° 5.051.534 (cuya descripción se incorpora en este documento como referencia) describe ciertos derivados de ciclopropiloxi-escualeno.

En el aspecto de combinación de esta invención puede usarse cualquier inhibidor de la escualeno ciclasa como segundo componente. La expresión inhibidor de la escualeno ciclasa se refiere a compuestos que inhiben la bioconversión de escualeno-2,3-epóxido en lanosterol, catalizada por la enzima escualeno ciclasa. Los especialistas en la técnica determinan fácilmente tal inhibición de acuerdo con ensayos convencionales (FEBS Lett. 1989; 244:347-350.). Además, los compuestos que se describen y a los que se hace referencia más adelante son inhibidores de la escualeno ciclasa, sin embargo, los especialistas en la técnica conocerán otros inhibidores de la escualeno ciclasa. La Publicación PCT WO9410150 (cuya descripción se incorpora en este documento como referencia) describe ciertos derivados de 1,2,3,5,6,7,8,8a-octahidro-5,5,8(beta)-trimetil-6-isoquinolinamina, tales como N-trifluoroacetil-1,2,3,5,6,7,8,8a-octahidro-2-alil-5,5,8(beta)-trimetil-6(beta)-isoquinolinamina. La publicación de patente francesa 2697250 (cuya descripción se incorpora como

referencia) describe ciertos derivados de beta,beta-dimetil-4-piperidina etanol tales como 1-(1,5,9-trimetildecil)-beta,beta-dimetil-4-piperidinetanol.

En el aspecto de combinación de esta invención puede usarse cualquier inhibidor combinado de la escualeno epoxidasa/escualeno ciclasa como segundo componente. La expresión inhibidor combinado de la escualeno epoxidasa/escualeno ciclasa se refiere a compuestos que inhiben la bioconversión de escualeno en lanoesterol mediante un intermedio escualeno-2,3-epóxido. En algunos ensayos no es posible distinguir entre inhibidores de la escualeno epoxidasa e inhibidores de la escualeno ciclasa, sin embargo, los especialistas reconocen estos ensayos. De esta forma, los especialistas en la técnica determinan fácilmente la inhibición mediante inhibidores combinados de la escualeno epoxidasa/escualeno ciclasa de acuerdo con los ensayos mencionados anteriormente para inhibidores de la escualeno ciclasa o escualeno epoxidasa. Más adelante se describe y se hace referencia a varios de estos compuestos, sin embargo, los especialistas en la técnica conocerán otros inhibidores combinados de la escualeno epoxidasa/ escualeno ciclasa. Las Patentes de Estados Unidos Nº 5.084.461 y 5.278.171 (cuyas descripciones se incorporan en este documento como referencia) describen ciertos derivados de azadecalina. La publicación EP 468.434 (cuya descripción se incorpora en este documento como referencia) describe ciertos derivados de éter de piperidilo y tio-éter tales como sulfóxido de 2-(1-piperidil)pentil isopentilo y sulfuro de 2-(1-piperidil)etil etilo. La publicación PCT WO 9401404 (cuya descripción se incorpora en este documento como referencia) describe ciertas acil-piperidinas tales como 1-(1-oxopentil-5-feniltio)-4-(2-hidroxi-1-metil)-etil)piperidina. La patente de Estados Unidos Nº 5.102.915 (cuya descripción se incorpora en este documento como referencia) describe ciertos derivados de ciclopropiloxi-escualeno.

Los compuestos de la presente invención también pueden administrarse en

combinación con compuestos naturales que actúan para reducir los niveles de colesterol en plasma. Estos compuestos naturales se denominan habitualmente nutracéuticos e incluyen, por ejemplo, extracto de ajo y niacina. Está disponible una forma de niacina de liberación lenta y se conooce como Niaspan. La niacina también puede combinarse con otros agentes terapéuticos tales como lovastatina, u otro es un inhibidor de la HMG-CoA reductasa. Esta terapia de combinación con lovastatina se conoce como ADVICOR™ (Kos Pharmaceuticals Inc.).

En el aspecto de combinación de la presente invención puede usarse cualquier inhibidor de absorción de colesterol. La expresión inhibidor de absorción de colesterol se refiere a la capacidad de un compuesto para evitar que el colesterol contenido en el lumen del intestino entre en las células intestinales y/o pase de las células intestinales al sistema linfático y/o al flujo sanguíneo. Los especialistas en la técnica determinan fácilmente tal inhibición de acuerdo con ensayos convencionales (por ejemplo, J. Lipid Res. (1993) 34: 377-395). Los especialistas en la técnica conocen los inhibidores de absorción de colesterol y se describen, por ejemplo, en el documento PCT WO 94/00480. Un ejemplo de un inhibidor de absorción de colesterol aprobado recientemente es ZETIA™ (ezetimibe) (Schering-Plough/Merck).

En el aspecto de la terapia de combinación de la presente invención puede usarse cualquier inhibidor de la ACAT. La expresión inhibidor de la ACAT se refiere a compuestos que inhiben la esterificación intracelular del colesterol dietético mediante la enzima acil CoA: colesterol aciltransferasa. El especialista en la técnica puede determinar fácilmente tal inhibición de acuerdo con ensayos convencionales, tales como el procedimiento de Heider y col. descrito en el *Journal of Lipid Research*, 24:1127 (1983). Los especialistas en la técnica conocen varios de estos compuestos, por ejemplo, la patente de Estados Unidos N° 5.510.379 describe ciertos carboxisulfonatos,

mientras que los documentos WO 96/26948 y WO 96/10559 describen derivados de urea que tienen actividad inhibidora de ACAT. Los ejemplos de inhibidores de la ACAT incluyen compuestos tales como Avasimibe (Pfizer), CS-505 (Sankyo) y Eflucimibe (Eli Lilly y Pierre Fabre).

En el aspecto de la terapia de combinación de la presente invención puede usarse cualquier inhibidor de lipasa. Un inhibidor de lipasa es un compuesto que inhibe la escisión de los triglicéridos dietéticos o de los fosfolípidos en plasma en ácidos grasos libres y en los correspondientes glicéridos (por ejemplo, EL, HL, etc). En condiciones fisiológicas normales, la lipólisis tiene lugar mediante un procedimiento de dos etapas que implica la acilación de un resto de serina activado de la enzima lipasa. Esto lleva a la producción de un intermedio hemiacetal de ácido graso-lipasa, que después se escinde para liberar un diglicérido. Después de la desacilación adicional, el intermedio de lipasa-ácido graso se escinde, dando lugar a lipasa libre, un glicérido y ácido graso. En el intestino, los ácidos grasos libres resultantes y los monoglicéridos se incorporan en las micelas de ácidos biliares-fosfolípidos, que se absorben posteriormente a nivel del borde en cepillo del intestino delgado. Las micelas eventualmente entran la circulación periférica en forma de quilomicrones. Los especialistas en la técnica determinan fácilmente tal actividad de la inhibición de lipasa de acuerdo con ensayos convencionales (por ejemplo, Methods. Enzymol. 286: 190-231).

La lipasa pancreática media la escisión metabólica de ácidos grasos a partir de triglicéridos en las posiciones 1- y 3-carbono. El sitio principal del metabolismo de las grasas ingeridas es en el duodeno y en el yeyuno proximal mediante la lipasa pancreática, que se segrega normalmente en gran exceso de a las cantidades necesarias para la ruptura de grasas en el intestino delgado superior. Como la lipasa pancreática es la enzima primaria que se necesita para la absorción de triglicéridos dietéticos, los

inhibidores tienen utilidad en el tratamiento de la obesidad y de otras enfermedades relacionadas. Los especialistas en la técnica determinan fácilmente tal actividad de la inhibición de lipasa pancreática de acuerdo con ensayos convencionales (por ejemplo, Methods. Enzymol. 286: 190-231).

La lipasa gástrica es una lipasa inmunológicamente distinta que es responsable aproximadamente del 10 al 40% de la digestión de las grasas dietéticas. La lipasa gástrica se segrega en respuesta a la estimulación mecánica, la ingestión de comida, la presencia de una comida grasa o por agentes simpáticos. La lipólisis gástrica de grasas ingeridas tiene una importancia fisiológica en el aprovisionamiento de ácidos grasos necesarios para activar la actividad de la lipasa pancreática en el intestino y también es importante para la absorción de grasas en varias afecciones fisiológicas y patológicas asociadas con la insuficiencia pancreática. Véase, por ejemplo, C.K. Abrams, y col., *Gastroenterology*, 92, 125 (1987). Los especialistas en la técnica determinan fácilmente tal inhibición de lipasa gástrica de acuerdo con ensayos convencionales (por ejemplo, Methods Enzymol. 286: 190-231).

Un especialista en la técnica conoce diversos inhibidores de lipasa gástrica y/o pancreática. Los inhibidores de lipasa preferidos son los inhibidores que se seleccionan entre el grupo compuesto por lipstatina, tetrahidrolipstatina (orlistat), valilactona, esterastina, ebelactona A y ebelactona B. Se prefiere especialmente el compuesto tetrahidrolipstatina. El inhibidor de lipasa, *N*-3-trifluorometilfenil-*N'*-3-cloro-4'-trifluorometilfenilurea, y los diversos derivados de urea relacionados con el mismo, se describen en la Patente de Estados Unidos Nº 4.405.644. El inhibidor de lipasa, esteracina, se describe en las Patentes de Estados Unidos Nº 4.189.438 y 4.242.453. El inhibidor de lipasa, ciclo-O,O'-[(1,6-hexanodiil)-bis-(iminocarbonil)]dioxima, y las diversas bis(iminocarbonil)dioximas relacionadas con el mismo pueden prepararse

como se describe en Petersen y col., *Liebig's Annalen*, 562, 205-229 (1949).

A continuación se describen varios inhibidores de lipasa pancreática. En la Patente de Estados Unidos Nº 4.598.089 se describen los inhibidores de lipasa pancreática lipstatina, lactona de ácido (2*S*, 3*S*, 5*S*, 7*Z*, 10*Z*)-5-[(*S*)-2-formamido-4-metil-valeriloxi]-2-hexil-3-hidroxi-7,10-hexadecanoico y tetrahidrolpstatina (orlistat), lactona de ácido (2*S*, 3*S*, 5*S*)-5-[(*S*)-2-formamido-4-metil-valeriloxi]-2-hexil-3-hidroxi-hexadecanoico y los distintos derivados sustituidos de *N*-formillleucina y esteroisómeros de los mismos. Por ejemplo, tetrahidrolipstatina se prepara como se describe en las Patentes de Estados Unidos Nº 5.274.143; 5.420.305; 5.540.917 y 5.643.874. El inhibidor de lipasa pancreática, FL-386, 1-[4-(2-metilpropil)ciclohexil]-2-[(fenilsulfonil)oxi-etanona, y los distintos derivados sulfonato sustituidos relacionados con el mismo, se describen en la Patente de Estados Unidos Nº 4.452.813. El inhibidor de lipasa pancreática, WAY-121898, 4-fenoxifenil-4-metilpiperidin-1-il-carboxilato, y los distintos ésteres de carbamato y sales farmacéuticamente aceptables relacionadas con los mismos, se describen en las Patentes de Estados Unidos Nº 5.512.565; 5.391.571 y 5.602.151. El inhibidor de lipasa pancreática, valilactona, y un proceso para la preparación del mismo mediante el cultivo microbiano de *Actinomycetes* cepa MG147-CF2, se describen en Kitahara, y col., *J. Antibiotics*, 40 (11), 1647-1650 (1987). Los inhibidores de lipasa pancreática, ebelactona A y ebelactona B, y un procedimiento para la preparación de los mismos mediante el cultivo microbiano de *Acitomycetes* cepa MG7-G1, se describen en Umezawa, y col., *J. Antibiotics*, 33, 1594-1596 (1980). El uso de ebelactonas A y B en la supresión de la formación de monoglicéridos se describe en la Patente japonesa Kokai 08-143457, publicada el 4 de Junio de 1996.

Otros compuestos que se comercializan para la hiperlipidemia, incluyendo hipercolesterolemia y que pretenden ayudar a prevenir o tratar la aterosclerosis incluyen

secuestradores de ácidos biliares, tales como Welchol®, Colestid®, LoCholest® y Questran®, y derivados de ácido fíbrico, tales como Atromid®, Lopid® y Tricor®.

La diabetes puede tratarse administrando a un paciente que tiene diabetes (especialmente de Tipo II), resistencia a la insulina, alteración a la tolerancia a la glucosa, síndrome metabólico o similares, o cualquiera de las complicaciones diabéticas tales como neuropatía, nefropatía, retinopatía o cataratas, una cantidad terapéuticamente eficaz de un compuesto de la presente invención en combinación con otros agentes (por ejemplo, insulina) que pueden usarse para tratar la diabetes. Esto incluye las clases de agentes anti-diabéticos (y agentes específicos) descritos en este documento.

Puede usarse cualquier inhibidor de glucógeno fosforilasa como segundo agente en combinación con un compuesto de la presente invención. La expresión inhibidor de glucógeno fosforilasa se refiere a compuestos que inhiben la bioconversión de glucógeno en glucosa-1-fosfato que se cataliza por la enzima glucógeno fosforilasa. Los especialistas en la técnica determinan fácilmente tal actividad de inhibición de glucógeno fosforilasa de acuerdo con ensayos convencionales (por ejemplo, J. Med. Chem. 41 (1998) 2934-2938). Los especialistas en la técnica conocen diversos inhibidores de glucógeno fosforilasa incluyendo los descritos en el documento WO 96/39384 y WO 96/39385.

Se puede usar cualquier inhibidor de aldosa reductasa en combinación con un compuesto de la presente invención. La expresión inhibidor de aldosa reductasa se refiere a compuestos que inhiben la bioconversión de glucógeno en sorbitol, que se cataliza por la enzima aldosa reductasa. Los especialistas en la técnica determinan fácilmente tal inhibición de aldosa reductasa de acuerdo con ensayos convencionales (por ejemplo, J. Malone, *Diabetes*, 29:861-864 (1980). "Red Cell Sorbitol, an Indicator of Diabetic Control"). Los especialistas en la técnica conocen diversos inhibidores de

aldosa reductasa.

Puede usarse cualquier inhibidor de sorbitol deshidrogenasa con un compuesto de la presente invención. La expresión inhibidor de sorbitol deshidrogenasa se refiere a compuestos que inhiben la bioconversión de sorbitol en fructosa que se cataliza mediante la enzima sorbitol deshidrogenasa. Los especialistas en la técnica determinan fácilmente tal actividad del inhibidor de sorbitol deshidrogenasa de acuerdo con ensayos convencionales (por ejemplo, Analyt. Biochem (2000) 280:329-331. Se conocen diversos inhibidores de sorbitol deshidrogenasa, por ejemplo, las patentes de Estados Unidos Nº 5.728.704 y 5.866.578 describen compuestos y un procedimiento para tratar o prevenir complicaciones diabéticas inhibiendo la enzima sorbitol deshidrogenasa.

Puede usarse cualquier inhibidor de glucosidasa en combinación con un compuesto de la presente invención. Un inhibidor de glucosidasa inhibe la hidrólisis enzimática de carbohidratos complejos con hidrolasas de glucósido, por ejemplo amilasa o maltasa, en azúcares simples biodisponibles, por ejemplo, glucosa. La rápida acción metabólica de las glucosidasas, particularmente después de la ingestión de altos niveles de carbohidratos, da lugar a un estado de hipoglucemia alimentaria que, en sujetos adiposos o diabéticos conduce a una mayor secreción de insulina, mayor síntesis de grasas y a una reducción en la degradación de grasas. Después de tales hiperglucemias habitualmente tiene lugar la hipoglucemia, debido a un aumento de los niveles de insulina presentes. Además, se sabe que el quimo que queda en el estómago promueve la producción de jugo gástrico, lo que inicia o favorece el desarrollo de gastritis o úlceras duodenales. Por consiguiente, se sabe que los inhibidores de glucosidasa son útiles en la aceleración del paso de carbohidratos a través del estomago y en la inhibición de la absorción de glucosa desde el intestino. Además, por lo tanto, la conversión de carbohidratos en lípidos del tejido graso y la posterior incorporación de

grasa de la alimentación en depósitos de tejido graso se reduce o se retrasa, con el beneficio concomitante de reducir o prevenir las anormalidades perjudiciales resultantes del mismo. Los especialistas en la técnica determinan fácilmente tal actividad de inhibición de glucosidasa de acuerdo con ensayos convencionales (por ejemplo, Biochemistry (1969) 8: 4214).

Un inhibidor de glucosidasa preferido generalmente incluye un inhibidor de amilasa. Un inhibidor de amilasa es un inhibidor de glucosidasa que inhibe la degradación enzimática del almidón o glucógeno en maltosa. Los especialistas en la técnica determinan fácilmente tal actividad de inhibición de amilasa de acuerdo con ensayos convencionales (por ejemplo, Methods Enzymol. (1955) 1: 149). La inhibición de tal degradación enzimática es beneficiosa en la reducción de las cantidades de azúcares biodisponibles, incluyendo glucosa y maltosa y las enfermedades perjudiciales concomitantes resultantes de la misma.

El especialista en la técnica conoce diversos inhibidores de glucosidasa y más adelante se proporcionan ejemplos. Son inhibidores preferidos de glucosidasa los inhibidores que se seleccionan entre el grupo compuesto por acarbose, adiposina, voglibosa, miglitol, emiglitato, camiglibosa, tendamistato, trestatina, pradimicin-Q y salbostatina. El inhibidor de glucosidasa, acarbosa, y los diversos derivados de aminoazúcar relacionados con el mismo se describen en las patentes de Estados Unidos Nº 4.062.950 y 4.174.439, respectivamente. El inhibidor de glucosidasa, adiposina, se describe en la patente de Estados Unidos Nº 4.254.256. El inhibidor de glucosidasa, voglibosa, 3,4-didesoxi-4-[[2-hidroxi-1-(hidroximetil)etil]amino]-2-*C*-(hidroximetil)-*D*-epi-inositol y los diversos pseudo aminoazúcares N-sustituidos relacionados con el mismo, se describen en la patente de Estados Unidos Nº 4.701.559. El inhibidor de glucosidasa, miglitol, (2*R*,3*R*,4*R*,5*S*)-1-(2-hidroxietil)-2-(hidroximetil)-3,4,5-

piperidintriol y las diversas 3,4,5-trihidroxipiperidinas relacionadas con el mismo, se describen en la patente de Estados Unidos N° 4.639.436. El inhibidor de glucosidasa, emiglitato, *p*-[2-[(2*R*,3*R*,4*R*,5*S*)-3,4,5-trihidroxi-2-(hidroximetil)piperidino]etoxi]-benzoato de etilo, los diversos derivados relacionados con el mismo y sales de adición de ácidos farmacéuticamente aceptables del mismo, se describen en la patente de Estados Unidos N° 5.192.772. El inhibidor de glucosidasa, MDL-25637, 2,6-didesoxi-7-O-β-D-glucopirano-silil-2,6-imino-D-glicero-L-gluco-heptitol, los diversos homodisacáridos relacionados con el mismo y las sales de adición de ácidos farmacéuticamente aceptables del mismo se describen en la patente de Estados Unidos N° 4.634.765. El inhibidor de glucosidasa, camiglibosa, sesquihidrato de 6-desoxi-[(2*R*,3*R*,4*R*,5*S*)-3,4,5-trihidroxi-2-(hidroximetil)piperidino]-α-D-glucopiranósido de etilo, los derivados desoxi-nojirimicina relacionados con el mismo, las diversas sales farmacéuticamente aceptables del mismo y procedimientos sintéticos para la preparación de los mismos se describen en las patentes de Estados Unidos N° 5.157.116 y 5.504.078. El inhibidor de glicosidasa, salbostatina y los diversos pseudosacáridos relacionados con el mismo, se describen en la Patente de Estados Unidos N° 5.091.524.

El especialista en la técnica conoce diversos inhibidores de amilasa. El inhibidor de amilasa, tendamistat y los diversos péptidos cíclicos relacionados con el mismo se describen en la patente de Estados Unidos N° 4.451.455. El inhibidor de amilasa AI-3688 y los diversos polipéptidos cíclicos relacionados con el mismo se describen en la patente de Estados Unidos N° 4.623.714. El inhibidor de amilasa, trestatina, que consiste en una mezcla de trestatina A, trestatina B y trestatina C y los diversos aminoazúcares que contienen trehalosa relacionados con el mismo se describen en la patente de Estados Unidos N° 4.273.765.

Los compuestos anti-diabéticos adicionales, que pueden usarse como segundo

agente en combinación con un compuesto de la presente invención, incluyen, por ejemplo, los siguientes: biguanidas (por ejemplo, metformin), secretagogos de insulina (por ejemplo, sulfonilureas y glinidas), glitazonas, agonistas de PPARγ no glitazona, agonistas de PPARβ, inhibidores de DPP-IV, inhibidores de PDE5, inhibidores de GSK-3, antagonistas de glucagón, inhibidores de f-1,6-BPase (Metabasis/Sankyo), GLP-1/análogos (AC 2993, también conocido como exendina-4), insulina e imitaciones de insulina (Merck natural products). Otros ejemplos incluyen inhibidores de PKC-β y trituradores de AGE.

Los compuestos de la presente invención pueden usarse en combinación con otros agentes anti-obesidad. Se puede usar cualquier agente anti-obesidad como segundo agente en las combinaciones y ejemplos que se proporcionan en este documento. Los especialistas en la técnica determinan fácilmente tal actividad anti-obesidad de acuerdo con ensayos convencionales conocidos en la técnica.

Los agentes anti-obesidad adecuados incluyen fenilpropanolamina, efedrina, pseudoefedrina, fentermina, agonistas del receptor adrenérgico β_3, inhibidores de la secreción de apolipoproteína B/proteína de transferencia de triglicéridos microsomal (apo-B/MTP), agonistas de MCR-4, agonistas de la colecistoquinina-A (CCK-A), inhibidores de la recaptación de monoamina (por ejemplo, sibutramina), agentes simpatomiméticos, agentes serotoninérgicos, antagonistas del receptor cannabinoide (por ejemplo, rimonabant (SR-141.716A)), agonistas de dopamina (por ejemplo, bromocriptina), análogos del receptor de la hormona estimuladora des melanocitos, agonistas de 5HT2c, antagonistas de la hormona que concentra melanina, leptina (la proteína OB), análogos de leptina, agonistas del receptor de leptina, antagonistas de galanina, inhibidores de lipasa (por ejemplo, tetrahidrolipstatina, es decir, orlistat), agonistas de bombesina, agentes anorécticos (por ejemplo, un agonista de bombesina),

antagonistas del neuropéptido-Y, tiroxina, agentes tiromiméticos, deshidroepiandrosteronas o análogos de las mismas, agonistas o antagonistas del receptor glucocorticoide, antagonistas del receptor de orexina, antagonistas de la proteína de unión a urocortina, agonistas del receptor del péptido-1 tipo glucagón, factores neurotróficos ciliares (por ejemplo, Axokine™), proteínas relacionadas con el gen agoutí humano (AGRP), antagonistas del receptor de grelina, antagonistas o agonistas inversos del receptor de histamina 3, agonistas del receptor neuromedina U y similares.

Puede usarse cualquier tiromimético como segundo agente en combinación con un compuesto de la presente invención. Los especialistas en la técnica determinan fácilmente tal actividad tiromimética de acuerdo con ensayos convencionales (por ejemplo, Atherosclerosis (1996) 126:53-63). Los especialistas en la técnica conocen diversos agentes tiromiméticos, por ejemplo los descritos en las patentes de Estados Unidos 4.766.121; 4.826.876; 4.910.305; 5.061.798; 5.284.971; 5.401.772; 5.654.468; y 5.569.674. Otros agentes anti-obesidad incluyen sibutramina que puede preparase como se describe en la patente de Estados Unidos Nº 4.929.629 y bromocriptina que puede prepararse como se describe en las patentes de Estados Unidos Nº 3.752.814 y 3.752.888.

Los compuestos de la presente invención también pueden usarse en combinación con otros agentes antihipertensivos. Se puede usar cualquier agente hipertensivo como segundo agente en la combinaciones y ejemplos que se proporcionan en este documento. Los especialistas en la técnica determinan fácilmente tal actividad antihipertensiva de acuerdo con ensayos convencionales (por ejemplo, mediciones de la presión sanguínea).

Los ejemplos de productos comercializados actualmente que contienen agentes

antihipertensivos incluyen bloqueantes de los canales de calcio, tales como Cardizem®, Adalat®, Calan®, Cardene®, Covera®, Dilacor®, DynaCirc®, Procardia XL®, Sular®, Tiazac®, Vascor®, Verelan ®, Isoptin®, Nimotop®, Norvasc® y Plendil®; inhibidores de la enzima de conversión de la angiotensina (ACE) tales como Accupril®, Altace®, Captopril®, Lotensin®, Mavik®, Monopril®, Prinivil®, Univasc®, Vasotec® y Zestril®.

La osteoporosis es una enfermedad sistémica del esqueleto, caracterizada por una baja masa de hueso y por el deterioro del tejido óseo, con un correspondiente aumento de la fragilidad de los huesos y de la susceptibilidad a la fractura. En los Estados Unidos, la afección afecta a más de 25 millones de personas y provoca más de 1,3 millones de fracturas cada año, incluyendo 500.000 fracturas de columna, 250.000 fracturas de cadera y 240.000 fracturas de muñeca anuales Las fracturas de cadera son la consecuencia más seria de la osteoporosis, con un 5-20% de pacientes que mueren al año y quedando incapacitados más de un 50% de supervivientes.

Los ancianos tienen un mayor riesgo de osteoporosis y, por tanto, se prevé que el problema aumentará significativamente con el envejecimiento de la población. Se prevé que la incidencia global de fracturas aumente tres veces durante los próximos 60 años y un estudio ha estimado que habrá 4,5 millones de fracturas de cadera en el 2050.

Las mujeres tienen mayor riesgo de osteoporosis que los hombres. Las mujeres experimentan una rápida aceleración de perdida de hueso durante los cinco años siguientes a la menopausia. Otros factores que aumentan el riesgo incluyen el hábito de fumar, el abuso del alcohol, estilo de vida sedentario y poca ingestión de calcio.

Los especialistas en la técnica reconocerán que pueden usarse agentes anti-reabsorción (por ejemplo, progestinas, polifosfonatos, bisfosfonato(s), agonistas/antagonistas de estrógenos, estrógenos, combinaciones de estrógenos/progestina, Premarin®, estrona, estriol o 17α- o 17β-etilinil estradiol) junto

con los compuestos de la presente invención.

Las progestinas ilustrativas están disponibles a partir de fuentes comerciales e incluyen: algestona actofenido, altrenogest, acetato de arradinona, acetato de anagestona, acetato de cloromadinona, cingestol, acetato de clogestona, acetato de clomegestona, acetato de delmadinona, desogestrel, dimetilesterona, didrogesterona, etilnerona, diacetato de etinodiol, etonogestrel, acetato de flurogestona, gestaclona, gestodeno, caproato de gestonorona, gestrinona, haloprogesterona, caproato de hidroxiprogesterona, levonorgestrel, linestrenol, medrogestona, acetato de medroxiprogesterona, acetato de melengestrol, diacetato de metinodiol, noretindrona, acetato de noretindrona, noretinodrel, norgestimate, norgestomet, norgestrel, fenpropionato de oxogestona, progesterona, acetato de quingestanol, quingestrona y tigestol.

Son progestinas preferidas medroxiprogesterona, noretindrona y noretinodrel.

Los polifosfonatos que inhiben la reabsorción ósea ilustrativos incluyen polifosfonatos del tipo descrito en la patente de Estados Unidos Nº 3.683.080, cuya descripción se incorpora en este documento como referencia. Son polifosfonatos preferidos difosfonatos geminales (también denominados bis-fosfonatos). El tiludronato disódico es un polifosfonato especialmente preferido. El ácido ibandrónico es un polifosfonato especialmente preferido.. El alendronato y resindronato son polifosfonatos especialmente preferidos. El ácido zoledrónico es un polifosfonato especialmente preferido. Otros polifosfonatos preferidos son el ácido 6-amino-1-hidroxi-hexiliden-bisfosfónico y el ácido 1-hidroxi-3(metilpentilamino)-propilide-bisfosfónico. Los polifosfonatos pueden administrarse en forma del ácido o de una sal de metal alcalino o una sal de metal alcalinotérreo soluble. Los ésteres hidrolizables de los polifosfonatos se incluyen igualmente. Los ejemplos específicos incluyen ácido etano-1-hidroxi-1,1-

difosfónico, ácido metano difosfónico, ácido pentano-1-hidroxi-1,1-difosfónico, ácido metano dicloro difosfónico, ácido metano hidroxi difosfónico, ácido etano-1-amino-1,1-difosfónico, ácido etano-2-amino-1,1-difosfónico, ácido propano-3-amino-1-hidroxi-1,1-difosfónico, ácido propano-*N,N*-dimetil-3-amino-1-hidroxi-1,1-difosfónico, ácido propano-3,3-dimetil-3-amino-1-hidroxi-1,1-difosfónico, ácido fenil amino metano difosfónico, ácido *N,N*-dimetilamino metano difosfónico, ácido *N*(2-hidroxietil) amino metano difosfónico, ácido butano-4-amino-1-hidroxi-1,1-difosfónico, ácido pentano-5-amino-1-hidroxi-1,1-difosfónico, ácido hexano-6-amino-1-hidroxi-1,1-difosfónico y ésteres y sales farmacéuticamente aceptables de los mismos.

En particular, los compuestos de esta invención pueden combinarse con un agonista/antagonista de estrógenos de mamífero. En el aspecto de combinación de esta invención puede usarse cualquier agonista/antagonista de estrógenos. La expresión agonista/antagonista de estrógenos se refiere a compuestos que se unen al receptor de estrógenos, inhiben el recambio de hueso y evitan la pérdida masa ósea. En particular, los agonistas de estrógenos se definen en este documento como compuestos químicos capaces de unirse a los sitios del receptor de estrógenos en el tejido de mamíferos e imitan las acciones de los estrógenos en uno o más tejidos. En este documento, los antagonistas de estrógenos se definen como compuestos químicos capaces de unirse a los sitios del receptor de estrógenos en tejidos de mamíferos, y de bloquear las acciones de los estrógenos en uno o más tejidos. Los especialistas en la técnica determinan fácilmente tales actividades de acuerdo con ensayos convencionales incluyendo ensayos de unión al receptor de estrógenos, procedimientos convencionales de histomorfométrica ósea y densitómetro y Eriksen E.F. y col., Bone Histomorphometry, Raven Press, Nueva York, 1994, páginas 1-74; Grier S.J. y col., The Use of Dual-Energy X-Ray Absorptiometry in Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner

H.W. y Fogelman I., The Evaluation of Osteoporosis: Dual Enery X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., Londres, 1994, páginas 1-296). Más adelante se describe y hace referencia a una diversidad de estos compuestos.

Otro agonista/antagonista de estrógenos preferido es el ácido 3-(4-(1,2-difenil-gut-1-enil)-fenil)-acrílico, que se describe en Willson y col., Endocrinology, 1997, 138,3901-3911.

Otro agonista/antagonista de estrógenos preferido es tamoxifeno: (etanamina, 2-(-4-(1-,2-difenil-1-butenil)fenoxi)-*N,N*-dimetil, (*Z*)-2-,2-hidroxi-1,2,3-propanotricarboxilato (1:1)) y compuestos relacionados que se describen en la patente de Estados Unidos Nº 4.536.516, cuya descripción se incorpora en este documento como referencia.

Otro compuesto relacionado es 4-hidroxi-tamoxifeno, que se describe en la patente de Estados Unidos Nº 4.623.660, cuya descripción se incorpora en este documento como referencia.

Un agonista/antagonista de estrógenos preferido es raloxifeno: (metanona, (6-hidroxi-2-(4-hidroxifenil)-benzo[b]tien-3-il)(4-(2-(1-piperidinil)etoxi)fenil)-clorhidrato) que se describe en la patente de Estados Unidos Nº 4.418.068, cuya descripción se incorpora en este documento como referencia.

Otro agonista/antagonista de estrógenos preferido es toremifeno: (etanamina, 2-(4-(4-cloro-1,2-difenil-1-butenil)fenoxi)-*N,N*-dimetil-, (*Z*)-, 2-hidroxi,1,2,3-propanotricarboxilato (1:1) que se describe en la patente de Estados Unidos Nº 4.996.225, cuya descripción se incorpora en este documento como referencia.

Otro agonista/antagonista de estrógenos preferido es centchroman: 1-(2-((4-(-metoxi-2,2-dimetil-3-fenil-chroman-4-il)-fenoxi)-etil)-pirrolidina, que se describe en la patente de Estados Unidos Nº 3.822.287, cuya descripción se incorpora en este

documento como referencia. También se prefiere levormeloxifeno.

Otro agonista/antagonista de estrógenos preferido es idoxifeno: (*E*)-1-(2-(4-(1-(4-yodo-fenil)-2-fenil-but-1-enil)-fenoxi)-etil)-pirrolidona, que se describe en la patente de Estados Unidos Nº 4.839.155, cuya descripción se incorpora en este documento como referencia.

Otro agonista/antagonista de estrógenos preferido es 2-(4-metoxi-fenil)-3-[4-(2-piperidin-1-il-etoxi)-fenoxi]-benzo[b]-tiofeno-6-ol que se describe en la patente de Estados Unidos Nº 5.488.058, cuya descripción se incorpora en este documento como referencia.

Otro agonista/antagonista de estrógenos preferido es 6-(4-hidroxi-fenil)-5-(4-(2-piperidin-1-il-etoxi)-bencil)-naftalen-2-ol, que se describe en la patente de Estados Unidos Nº 5.484.795, cuya descripción se incorpora en este documento como referencia.

Otro agonista/antagonista de estrógenos preferido es (4-(2-(2-aza-biciclo[2.2.1]hept-2-il)-etoxi)-fenil)-(6-hidroxi-2-(4-hidroxi-fenil)-benzo[b]tiofen-3-il)-metanona, que se describe, junto con procedimientos de preparación, en la publicación PCT Nº WO 95/10513 asignada a Pfizer Inc.

Otros agonistas/antagonistas de estrógenos preferidos incluyen los compuestos TSE-424 (Wyeth-Ayerst Laboratories) y arazoxifeno.

Otros agonistas/antagonistas de estrógenos preferidos incluyen compuestos como los descritos en la patente de Estados Unidos 5.552.412 de cesión común con la presente, cuya descripción se incorpora en este documento como referencia. Son compuestos especialmente preferidos descritos en ese documento:

cis-6-(4-fluoro-fenil)-5-(4-(2-piperidin-1-il-etoxi)-fenil-5,6,7,8-tetrahidro-naftalen-2-ol;

(-)-*cis*-6-fenil-5-(4-(2-pirrolidin-1-il-etoxi)-fenil-5,6,7,8-tetrahidro-naftalen-2-ol (también conocido como lasofoxifeno);

cis-6-fenil-5-(4-(2-pirrolidin-1-il-etoxi)-fenil-5,6,7,8-tetrahidro-naftalen-2-ol;

cis-1-(6'-pirrilodinoetoxi-3'-piridil)-2-fenil-6-hidroxi-1,2,3,4-tetrahidronaftaleno.

1-(4'-pirrilodinoetoxifenil)-2-(4"-fluorofenil)-6-hidroxi-1,2,3,4-tetrahidronisoquinolina.

cis-6-(4-hidroxifenil)-5-(4-(2-piperidinil-1-il-etoxi)-fenil-5,6,7,8-tetrahidro-naftalen-2-ol;

1-(4'-pirrilodinoetoxifenil)-2-fenil-6-hidroxi-1,2,3,4-tetrahidroisoquinolina.

Otros agonistas/antagonistas de estrógenos se describen en la patente de Estados Unidos 4.133.814 (cuya descripción se incorpora en este documento como referencia). La patente de Estados Unidos 4.133.814 describe derivados de 2-fenil-3-aroil-benzotiofeno y 2-fenil-3-aroilbenzotiofen-1-óxido.

Otros agentes anti-osteoporosis, que pueden usarse como segundo agente en combinación con un compuesto de la presente invención incluyen, por ejemplo, los siguientes: hormona paratiroide (PTH) (un agente anabólico del hueso); secretagogos de la hormona paratiroide (PTH) (véase, por ejemplo, la patente de Estados Unidos N° 6.132.774), particularmente los antagonistas del receptor de calcio; calcitonina y vitamina D y análogos de la vitamina D.

Se puede usar cualquier modulador selectivo del receptor de andrógenos (SARM) en combinación con un compuesto de la presente invención. Un modulador selectivo del receptor de andrógenos (SARM) es un compuesto que posee actividad androgénica y que ejerce efectos selectivos en tejidos. Los compuestos SARM pueden funcionar como agonistas del receptor de andrógenos, agonistas parciales, antagonistas parciales o antagonistas. Los ejemplos de SARM adecuados incluyen compuestos tales

como acetato de ciproterona, clormadinona, flutamida, hidroxiflutamida, bicalutamida, nilutamida, espironolactona, derivados de 4-(trifluorometil)-2(1*H*)-pirrolidino[3,2-g]quinolinona, derivados de 1,2-dihidropiridino[5,6-g]quinolina y derivados de piperidino[3,2-g]quinolinona.

Cipterona, también conocida como (1b,2b)-6-cloro-1,2-dihidro-17-hidroxi-3'*H*-ciclopropa[1,2]pregna-1,4,6-trien-3,20-diona, se describe en la patente de Estados Unidos 3.234.093. Clormadinona, también conocida como 17-(acetiloxi)-6-cloropregna-4,6-dien-3,20-diona, en su forma de acetato, actúa como anti-andrógenos y se describe en la patente de Estados Unidos 3.485.852. Nilutamida, también conocida como 5,5-dimetil-3-[4-nitro-3-(trifluorometil)fenil]-2,4-imidazolidinadiona y por el nombre comercial Nilandron® se describe en la patente de Estados Unidos 4.097.578. Flutamida, también conocida como 2-metil-*N*-[4-nitro-3-(trifluorometil)fenil]propanamida y con el nombre comercial Eulexin® se describe en la patente de Estados Unidos 3.847.988. Bicalutamida, también conocida como 4'-ciano-a',a',a'-trifluoro-3-(4-fluorofenilsulfonil)-2-hidroxi-2-metilpropiono-m-toluidida y con el nombre comercial Casodex® se describe en el documento EP-100172. Los enantiómeros de biclutamida se describen por Tucker y Chesterton, *J. Med. Chem.* 1988, 31, 885-887. Se ha sugerido que hidroxiflutamida, un conocido antagonista del receptor de andrógenos en la mayoría de los tejidos, funciona como un SARM para los efectos en la producción de IL-6 por los osteoblastos, como se describe en Hofbaufer y col., *J. Bone Miner. Res* 1999, 14, 1330-1337. Se han descrito adicionalmente SARM en la patente de Estados Unidos 6.017.924; WO 01/16108, WO 01/16133, WO 01/16139, WO 02/00617, WO 02/16310, publicación de solicitud de patente de Estados Unidos Nº US 2002/0099096, publicación de solicitud de patente de Estados Unidos Nº US 2003/0022868, WO 03/011302 y WO 03/011824. Todas las referencias anteriores se

incorporan en este documento como referencia.

Los materiales y reactivos de partida para los compuestos descritos anteriormente también están disponibles fácilmente o pueden sintetizarse fácilmente por parte de los especialistas en la técnica usando procedimientos convencionales de síntesis orgánica. Por ejemplo, muchos de los compuestos usados en este documento, se refieren, o se derivan de compuestos sobre los que existe un gran interés científico y necesidad comercial y, por consiguiente, muchos de estos compuestos están disponibles en el mercado o están descritos en la bibliografía o se preparan fácilmente a partir de otras sustancias habitualmente disponibles mediante procedimientos descritos en la bibliografía.

Algunos de los compuestos de esta invención o intermedios en su síntesis tienen átomos de carbono asimétricos y, por lo tanto, son enantiómeros o diastereómeros. Las mezclas diastereoméricas pueden separarse en sus diastereómeros individuales en función de sus diferencias fisicoquímicas mediante procedimientos conocidos per se, por ejemplo, por cromatografía y/o cristalización fraccionada. Los enantiómeros pueden separarse, por ejemplo, por procedimientos de HPLC quiral o transformando la mezcla enantiomérico en una mezcla diastereomérica mediante la reacción con un compuesto apropiado ópticamente activo (por ejemplo, alcohol), separando los diastereómeros y transformando (por ejemplo, hidrolizando) los diastereómeros individuales en los correspondientes enantiómeros puros. Además, una mezcla enantiomérica de los compuestos o un intermedio en su síntesis que contiene un resto ácido o básico puede separarse en sus correspondientes enantiómeros puros formando una sal diastereomérica con un ácido o base quiral ópticamente puro (por ejemplo, 1-fenil-etil amina o ácido tartárico) y separando los diastereoisómero por cristalización fraccionada seguido de neutralización para romper la sal, proporcionando, de esta forma, los correspondientes

enantiómeros puros. Todos estos isómeros, incluyendo diastereómeros, enantiómeros y mezclas de los mismos, se consideran parte de esta invención para todos los compuestos de la presente invención, incluyendo los compuestos de la presente invención. Además, algunos de los compuestos de esta invención son atropisómeros (por ejemplo, biarilos sustituidos) y se consideran parte de esta invención.

Más específicamente, los compuestos de esta invención pueden obtenerse en forma enantioméricamente enriquecida resolviendo el racemato del compuesto final o un intermedio en su síntesis, empleando cromatografía (preferiblemente cromatografía líquida a alta presión [HPLC] o una resina asimétrica (preferiblemente Chiralcel™ AD U OD (obtenida DE Chiral Technologies, Exton, Pensilvania)) con una fase móvil que consiste en un hidrocarburo (preferiblemente heptano o hexano) que contiene entre el 0 y el 50% de isopropanol (preferiblemente entre el 2 y el 20%) y entre el 0 y el 5% de una alquilamina (preferiblemente el 0,1% de dietilamina). La concentración de las fracciones que contienen el producto da lugar a los materiales deseados.

Algunos de los compuestos de esta invención son ácidos y forman una sal con un catión farmacéuticamente aceptable. Algunos de los compuestos de esta invención son básicos y forman una sal con un anión farmacéuticamente aceptable. Todas estas sales están dentro del alcance de esta invención y pueden prepararse mediante procedimientos convencionales tales como combinar las entidades básicas y ácidas, normalmente en una relación estequiométrica en un medio acuoso, no acuoso o parcialmente acuoso, según sea apropiado. Las sales se recuperan por filtración, precipitación con un no-disolvente seguido de filtración, por evaporación del disolvente, o, en el caso de las soluciones acuosas, por liofilización, según sea apropiado. Los compuestos pueden obtenerse en forma cristalina por disolución en un disolvente o disolventes apropiados tales como etanol, hexanos o mezclas de etanol/agua.

Además, cuando los compuestos de esta invención forman hidratos o solvatos también están incluidos dentro del alcance de la invención.

Los compuestos de esta invención, sus profármacos y las sales de tales compuestos y profármacos, están adaptados al uso terapéutico como agentes que inhiben la actividad de la proteína de transferencia del éster de colesterol en mamíferos, particularmente en seres humanos. De esta forma, los compuestos de esta invención aumentan el colesterol HDL en plasma, sus componentes asociados y las funciones realizadas por ellos en mamíferos, particularmente en seres humanos. En virtud de su actividad, estos compuestos también reducen los niveles en plasma de triglicéridos, colesterol VLDL, Apo-B, colesterol LDL y sus componentes asociados en mamíferos, particularmente seres humanos. Además, estos compuestos son útiles a la hora de igualar el colesterol LDL y el colesterol HDL. Por lo tanto, estos compuestos son útiles para el tratamiento y la corrección de las diversas dislipidemias que se observa que se asocian con el desarrollo y la incidencia de aterosclerosis y de enfermedades cardiovasculares, incluyendo enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipertrigliceridemia, hipercolesterolemia, hipercolesterolemia familiar, HDL bajo y componentes asociados, LDL alto y componentes asociados, Lp(a) alto, LDL alto de baja densidad, VLDL alto y componentes asociados y lipemia post-prandial.

Además, la introducción de un gen funcional CETP en un animal que carece de CETP (ratón) tiene como resultado menores niveles de HDL (Agellon, L.B. y col: *J. Biol. Chem.* (1991) 266:10796-10801) y una mayor susceptibilidad a la aterosclerosis (Marotti, K.R. y col: *Nature* (1993) 364: 73-75). Además, la inhibición de la actividad CETP con un anticuerpo inhibidor aumenta el colesterol HDL en hámsters (Evans, G.F.,

y col: *J. of Lipid Research* (1994) 35: 1634-1645) y conejos (Whitlock, M.E. y col: *J. Clin. Invest.* (1989) 84: 129-137). La supresión del aumento de CETP en plasma mediante inyección intravenosa con ARNm con oligodesoxinucleótidos antisentido contra ARNm de CETP redujo la aterosclerosis en conejos alimentados con colesterol (Sugano, M., y col: *J. Biol. Chem.* (1988) 273:5033-5036.). De forma destacada, los sujetos humanos con una deficiencia de CETP en plasma, debido a una mutación genética tienen niveles notablemente elevados de colesterol HDL en plasma y apolipoproteína A.I, el principal componente apoproteico de HDL. Además, la mayoría muestran niveles marcadamente menores de colesterol LDL en plasma y apolipoproteína B (el principal componente aproproteico de LDL). (Inazu, A., Brown, M.L., Hesler, C.B., y col.: *N. Engl. J. Med.* (1990) 323: 1234-1238.).

Dada la correlación negativa entre los niveles de colesterol HDL y lipoproteínas asociadas a HDL y la correlación positiva entre triglicéridos, colesterol LDL y sus apolipoproteínas asociadas en sangre con el desarrollo de enfermedades cardiovasculares, cerebrovasculares y vasculares periféricas, los compuestos de esta invención, sus profármacos y las sales de tales compuestos y profármacos, por medio de su acción farmacológica, son útiles para la prevención, interrupción y/o regresión de la aterosclerosis y sus estados de enfermedad asociados. Estos incluyen trastornos cardiovasculares (por ejemplo, angina, isquemia, isquemia cardiaca e infarto de miocardio), complicaciones debidas a terapias de enfermedades cardiovasculares (por ejemplo, lesión por reperfusión y reestenosis angioplástica), hipertensión, alto riesgo cardiovascular asociado con hipertensión, ataques, aterosclerosis asociada con transplante de órganos, enfermedad cerebrovascular, disfunción cognitiva (incluyendo, sin limitación, demencia secundaria a la aterosclerosis, ataques isquémicos cerebrales pasajeros, neurodegeneración, deficiencia neuronal y retraso en la aparición o progreso

de la enfermedad de Alzheimer), altos niveles de estrés oxidativo, altos niveles de la proteína reactiva C, Síndrome Metabólico y altos niveles de HbA1C.

Debido a los efectos beneficiosos ampliamente asociados con niveles elevados de HDL, un agente que inhibe la actividad CETP en seres humanos, por medio de su capacidad para aumentar HDL, también proporciona medios valiosos para terapia en otras áreas de enfermedad.

De esta forma, dada la capacidad de los compuestos de esta invención, sus profármacos y las sales de tales compuestos y profármacos para alterar la composición de lipoproteínas mediante la inhibición de la transferencia del éster de colesterol, éstos se usan en el tratamiento de complicaciones vasculares asociadas con la diabetes, anormalidades lipoproteicas asociadas con diabetes y disfunción sexual asociada con diabetes y enfermedad vascular. La hiperlipidemia está presente en la mayoría de los sujetos con diabetes mellitus (Howard, B.V., 1987, J. Lipid. Res. 28, 613). Incluso en presencia de niveles normales de lípidos, los sujetos diabéticos experimentan un mayor riesgo de enfermedad cardiovascular (Kannel, W.B. y McGee, D.L. 1979, Diabetes Care 2, 120). Se sabe que la transferencia de éster de colesterol mediada por CTP se aumenta de forma anormal tanto en la diabetes dependiente de insulina (Bagdade, J.D., Subbaiah, P.V. y Ritter, M.C. 1991. Eur. J. Clin. Invest. 21, 161) como en la diabetes no dependiente de insulina (Bagdade. J.D., Ritter, M.C., Lane, J. y Subbaiah. 1993. Atherosclerosis 104, 69). Se ha sugerido que el aumento anormal en la transferencia de colesterol tiene como resultado cambios en la composición lipoproteica, particularmente para VLDL y LDL, que son más aterogénicas (Bagdade, J.D., Wagner, J.D., Rudel, L.L., y Clarkson, T.B. 1995 J. Lipid Res. 36, 759). Estos cambios no se observan necesariamente durante la exploración rutinaria de lípidos. De esta forma, la presente invención será útil en la reducción del riesgo de complicaciones cardiovasculares como

resultado de la afección diabética.

Los agentes descritos son útiles en el tratamiento de la obesidad y del alto riesgo cardiovascular asociado con la obesidad. Tanto en seres humanos (Radeau, T., Lau, P., Robb, M., McDonnell, M., Alihaud, G., y McPherson, R., 1995 *Journal of Lipid Research.* 36 (12):2552-61) como en primates no humanos (Quinet, E., Tall, A., Ramakrishnan, R., y Rudel, L., 1991. *Journal of Clinical Investigation.* 87 (5):1559-66) el ARNm de CETP se expresa a altos niveles en el tejido adiposo. El mensaje adiposo aumenta con la ingestión de grasas (Martin, L. J., Connelly, P.W., Nancoo, D., Wood, N., Zhang, Z.J., Maguire, G., Quinet, E., Tall, A.R., Marcel, Y.L. y McPherson, R., 1993 *Journal of Lipid Research.* 34 (3):437-46) y se traduce en proteína de transferencia funcional y a través de la secreción contribuye de forma significativa a los niveles de CETP en plasma. En los adipocitos humanos, la mayor parte del colesterol se proporciona por la LDL y HDL en plasma (Fong, B. S., y Angel, A., 1989. *Biochimica et Biophysica Acta.* 1004 (1):53-60. La captura del éster de colesterol HDL depende en gran parte de CETP (Benoist, F., Lau, P., McDonnell, M., Doelle, H., Milne, R., y McPherson. R., 1997 *Journal of Biological Chemistry.* 272 (38)23572-7). Esta capacidad de CETP para estimular la captura de colesterol HDL, junto con la mejor unión de HDL a los adipocitos en sujetos obesos (Jimenez, J. G., Fong, B., Julien, P., Despres, J. P., Rotstein, L., y Angel, A., 1989 *International Journal of Obesity.* 13 (5):699-709) sugiere que un papel de CETP, no solo generando el fenotipo de bajo HDL de estos sujetos, sino en el desarrollo de la propia obesidad promoviendo la acumulación de colesterol. Por lo tanto, los inhibidores de la actividad CETP que bloquean este procedimiento sirven como adyuvantes útiles en la terapia dietética causando una reducción de peso.

Los inhibidores de CETP son útiles en el tratamiento de la inflamación debido a

la sepsis gram negativa y choque séptico. Por ejemplo, la toxicidad sistémica de la sepsis Gram negativa se debe en gran parte a endotoxina, un lipopolisacárido (LPS) liberado de la superficie exterior de las bacterias, que causa una gran respuesta inflamatoria. El lipopolisacárido puede formar complejos con lipoproteínas (Ulevitch, R.J., Johnston, A.R. y Weinstein, D.B., 1981 J. Clin. Invest. 67, 827-37). Los estudios in vitro han demostrado que la unión de LPS a HDL reduce sustancialmente la producción y liberación de mediadores de la inflamación (Ulevitch, R.J., Johnston, A.R., 1978. J. Clin. Invest. 62, 1313-24). Los estudios in vivo demuestran que los ratones transgénicos que expresan apo-Al humana y altos niveles de HDL están protegidos del choque séptico (Levine, D.M., Parker, T.S., Donnelly, T.M., Walsh, A.M. y Rubin, A.L. 1993. Proc. Natl. Acad. Sci. 90, 12040-44). De forma destacada, la administración de HDL reconstituido a seres humanos expuestos con endotoxina tuvo como resultado una disminución de la respuesta inflamatoria (Pajkrt, D., Doran, J.E., Koster, F., Lerch, P.G., Arnet, B., van der Pol, T., ten Cate, J.W., y van Deventer, S.J.H. 1996. J. Exp. Med. 184, 1601-08). Los inhibidores de CETP, debido al hecho de que aumentan los niveles de HDL, atenúan el desarrollo de la inflamación y del choque séptico. Estos compuestos también serían útiles en el tratamiento de la endotoxemia, enfermedades autoinmunes y otras indicaciones de enfermedades sistémicas, rechazo al trasplante de órganos o tejidos y cáncer.

La utilidad de los compuestos de la invención, sus profármacos y las sales de tales compuestos como agentes médicos en el tratamiento de las enfermedades/afecciones descritas anteriormente en mamíferos (por ejemplo, seres humanos, hombres o mujeres) se demuestra mediante la actividad de los compuestos de esta invención en ensayos convencionales y en el ensayo *in vivo* descrito más adelante. El ensayo *in vivo* (con modificaciones apropiadas dentro de la capacidad del especialista

en la técnica) puede usarse para determinar la actividad de otros agentes que controlan lípidos o triglicéridos así como de los compuestos de esta invención. El protocolo de combinación descrito más adelante es útil para demostrar la utilidad de las combinaciones de agentes de lípidos y triglicéridos (por ejemplo, los compuestos de esta invención) descritos en este documento. Tales ensayos proporcionan también medios por los que se pueden comparar las actividades de los compuestos de esta invención, sus profármacos y las sales de tales compuestos y profármacos (o los demás agentes descritos en este documento) entre sí y con las actividades de otros compuestos conocidos. Los resultados de estas comparaciones son útiles para determinar los niveles de dosificación en mamíferos, incluyendo seres humanos, para el tratamiento de tales enfermedades.

Por supuesto, los especialistas en la técnica pueden variar los protocolos que se muestran más adelante.

La actividad hiperalfacolesterolémica de los compuestos puede determinarse evaluando el efecto de estos compuestos sobre la acción de la proteína de transferencia del éster de colesterol midiendo la velocidad relativa de transferencia de lípidos radiomarcados entre fracciones lipoproteicas, esencialmente como ha descrito previamente por Morton en J. Biol. Chem. 256, 11992, 1981 y por Dias en Clin. Chem. 34, 2322, 1988.

ENSAYO *IN VITRO* DE CETP

A continuación se proporciona una breve descripción de ensayos de transferencia de éster de colesterol en plasma humano al 97% (entero) o diluido (*in vitro*) y en plasma animal (*ex vivo*): se evalúa la actividad CETP en presencia o ausencia de fármaco determinando la transferencia de oleato de colesterol (CO) marcado con ^{3}H desde el indicador exógeno HDL o LDL a la fracción de lipoproteína HDL o no-HDL

en plasma humano, respectivamente, o desde la fracción de LDL marcado con ^{3}H a la fracción HDL en plasma animal. Se preparan sustratos lipoproteicos humanos marcados de forma similar al procedimiento descrito por Morton en el que se emplea la actividad endógena de CETP en plasma para transferir ^{3}H-CO de los liposomas fosfolipídicos a todas las fracciones de lipoproteína en el plasma. Posteriormente se aísla LDL y HDL marcadas con ^{3}H mediante ultracentrifugación secuencial con cortes de densidad de 1,019-1,063 y 1,10-1,21 g/ml, respectivamente.

Para el ensayo de la actividad en plasma al 97% o completo, se añade HDL ^{3}H - marcado al plasma a 10-25 nmoles de CO/ml y las muestras se incuban a 37°C durante 2,5-3 horas. Después se precipitan lipoproteínas no-HDL mediante la adición de un volumen igual de polietilenglicol 8000 (Dias) al 20% (p/vol). Las muestras se centrifugan a 750 g x 20 minutos y la radiactividad contenida en el sobrenadante que contiene HDL se determina mediante recuento de escintilación líquida. La introducción de diversas cantidades de los compuestos de esta invención en forma de solución en dimetilsulfóxido en plasma humano antes de añadir el oleato de colesterol radiomarcado y la comparación de las cantidades de radiomarcaje transferidas en comparación con las incubaciones que no contienen compuestos inhibidores permiten que se determinen las actividades inhibidoras de transferencia de éster de colesterol.

Cuando se desea un ensayo más sensible, se utiliza un ensayo in vitro que usa plasma humano diluido. Para este ensayo, se añade LDL marcada con ^{3}H al plasma a 50 nmoles de CO/ml y las muestras se incuban a 37°C durante 7 horas. Después, se precipitan lipoproteínas no-HDL mediante la adición de fosfato de potasio hasta una concentración final de 100 mM seguido de cloruro de manganeso hasta una concentración final de 20 mM. Después de agitar vorticialmente, las muestras se centrifugan a 750 g x 20 minutos y la radiactividad contenida en el sobrenadante que

contiene HDL se determina mediante recuento de escintilación líquida. La introducción de diversas cantidades de los compuestos de esta invención en forma de solución en dimetilsulfóxido en plasma humano diluido antes de la adición del oleato de colesterol radiomarcado y la comparación de las cantidades de radiomarcaje transferidas en comparación con las incubaciones que no contienen compuestos inhibidores permiten que se determinen las actividades inhibidoras de transferencia de éster de colesterol. Este ensayo se ha adaptado para realizarse en un formato de placa de microtitulación mediante recuento de escintilación líquida realizado usando un lector de placas Wallac.

ENSAYO IN VIVO DE CETP

La actividad *in vivo* de estos compuestos se puede determinar por la cantidad de agente que se tiene que administrar, con relación al control, para inhibir la actividad de transferencia del éster de colesterol en un 50% en diversos puntos temporales *ex vivo* o para aumentar el colesterol HDL mediante un porcentaje dado en una especie animal que contiene CETP. Pueden usarse ratones transgénicos que expresan tanto CETP humano como apolipoproteína Al (Charles River, Boston, MA) para evaluar compuestos *in vivo*. Los compuestos a examinar se administran mediante sonda oral en un vehículo de emulsión que contiene aceite de oliva al 20% (v/v) y taurocolato sódico al 80% (0,5%). Si se desea una muestra de sangre de predosis, se extrae sangre de ratones retroorbitalmente antes de la dosificación. En diversos períodos de tiempo después de la dosificación, que varían de 4 horas a 24 horas, los animales se sacrifican, se obtiene la sangre por punción en el corazón y se miden los parámetros de lípidos, incluyendo el colesterol total, colesterol HDL y LDL y los triglicéridos. La actividad CETP se determina mediante un procedimiento similar al descrito anteriormente con la excepción de que se usa LDL que contiene oleato de colesterol marcado con ^{3}H como la fuente donadora en vez de HDL. Los valores obtenidos para los lípidos y la actividad de

transferencia se comparan con los obtenidos antes de la dosificación y/o los de los ratones que reciben solamente vehículo.

ENSAYO DE LÍPDOS EN PLASMA

La actividad de estos compuestos también puede demostrarse determinando la cantidad de agente requerido para alterar niveles de lípidos en plasma, por ejemplo los niveles de colesterol HDL, los niveles de colesterol LDL, los niveles de colesterol VLDL o los niveles de triglicéridos, en el plasma de ciertos mamíferos, por ejemplo los titi que poseen actividad CETP y un perfil de lipoproteína en plasma similar al de los seres humanos (Crook y col. Arteriosclerosis 10, 625, 1990). Los titi adultos se asignan a grupos de tratamiento de forma que cada grupo tenga una media ± DT similar para concentraciones de colesterol total, HDL y/o LDL en plasma. Después de la asignación del grupo, a los titi se les administra dosis diarias con compuesto en forma de mezcla dietética o por intubación intragástrica durante uno a ocho días. Los titi de control reciben sólo vehículo de dosificación. Los valores de colesterol total, LDL, VLDL y HDL en plasma pueden determinarse en cualquier momento durante el estudio obteniendo sangre de una vena antecubital y separando las lipoproteínas en plasma en sus subclases individuales mediante centrifugación con gradiente de densidad y midiendo la concentración de colesterol como se ha descrito previamente (Crook y col. Arteriosclerosis 10, 625, 1990).

ENSAYO IN VIVO DE ATEROSCLEROSIS

Los efectos anti-ateroscleróticos de los compuestos pueden determinarse por la cantidad de compuesto requerido para reducir la deposición de lípidos en la aorta de conejos. Se alimentan conejos machos New Zealand White con una dieta que contiene colesterol al 0,2% y aceite de coco al 10% durante 4 días (se alimentan una vez al día). Se toman muestras de sangre de conejos a partir de la vena marginal del oído y se

determinan los valores de colesterol total en plasma a partir de estas muestras. Después, los conejos se asignan a grupos de tratamiento de forma que cada grupo tiene una media ± DT similar para la concentración total de colesterol en plasma, concentración de colesterol HDL, concentración de triglicéridos y/o actividad de la proteína de transferencia del éster de colesterol. Después de la asignación del grupo, a los conejos se les administra una dosis diaria con compuesto dado en forma de mezcla dietética o en un pequeño trozo de dulce basado en gelatina. Los conejos de control reciben sólo el vehículo de dosificación, ya sea comida o dulce en gelatina. La dieta de colesterol/aceite de coco continúa junto con la administración del compuesto a lo largo del estudio. Los valores de colesterol en plasma y de la actividad de proteína de transferencia del éster de colesterol pueden determinarse en cualquier momento durante el estudio obteniendo sangre de la vena marginal del oído. Después de 3-5 meses, los conejos se sacrifican y las aortas se retiran del arco torácico a la rama de las arterias ilíacas. Se quita la adventicia de las aortas, se abren longitudinalmente y después se analizan pigmentadas o no con Sudan IV como se describe por Holman y col. (Lab. Invest. 1958, 7, 42-47). El porcentaje de área de superficie lesionada se cuantifica por densitometría usando un Optimas Image Analyzing System (sistemas de procesamiento de la imagen). La reducción de la deposición de lípidos se indica mediante una reducción en el porcentaje de área de superficie lesionada en el grupo que recibe el compuesto en comparación con los conejos de control.

PROTOCOLO ANTIOBESIDAD

La capacidad de los inhibidores de CETP para causar pérdida de peso puede evaluarse en sujetos humanos obesos con índice de masa corporal (BMI) ≥ 30 kg/m^2. Las dosis del inhibidor se administran de forma suficiente para producir un aumento de $\geq 25\%$ en los niveles de colesterol HDL. El BMI y la distribución de la grasa corporal

definida como la relación (WHR) entre cintura (W) y cadera (H), se controlan durante el curso de los estudios de 3-6 meses y los resultados para los grupos de tratamiento se comparan con aquellos que reciben placebo.

ENSAYO DE SEPSIS IN VIVO

Los estudios *in vivo* demuestran que los ratones transgénicos que expresan apo-Al humana y niveles elevados de HDL están protegidos contra el choque séptico. De esta forma, la capacidad de los inhibidores de CETP para proteger contra el choque séptico puede demostrarse en ratones transgénicos que expresan tanto apo-Al humana como transgenes humanos de CETP (Levine, D. M., Parker, T.S., Donnelly, T.M., Walsh, A. M. y Rubin, A.L., 1993, Proc. Natl. Acad. Sci. 90, 12040-44). Se administra LPS derivada de *E. coli* a 30 mg/kg por inyección i.p. a animales a los que se les ha administrado un inhibidor de CETP en una dosis apropiada para producir un aumento de HDL. El número de ratones supervivientes se determina en períodos de tiempo de hasta 48 horas después de la inyección de LPS y se compara con los ratones a los que sólo se les ha administrado vehículo (menos inhibidor de CETP).

La administración de los compuestos de esta invención puede realizarse mediante cualquier procedimiento que administra un compuesto de esta invención por vía sistémica y/o localmente. Estos procedimientos incluyen vías orales, parenterales, intraduodenales, etc. Generalmente, los compuestos de esta invención se administran oralmente, aunque se puede utilizar administración parenteral (por ejemplo, por vía intravenosa, intramuscular, subcutánea o intramedular), por ejemplo, cuando la administración oral no es apropiada para el objetivo perseguido o cuando el paciente es incapaz de ingerir el fármaco.

En general se usa una cantidad de un compuesto de esta invención que es suficiente para conseguir el efecto terapéutico deseado (por ejemplo, aumento del nivel

de HDL).

En general, una dosificación eficaz para los compuestos de esta invención es de aproximadamente 0,001 a 100 mg/kg/día del compuesto, un profármaco del mismo o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco. Una dosificación especialmente preferida es de aproximadamente 0,01 a 10 mg/kg/día del compuesto, un profármaco del mismo o una sal farmacéuticamente aceptable de dicho compuesto o dicho profármaco.

Se usa una dosificación de los agentes farmacéuticos de combinación a usar junto con los inhibidores de CETP que es eficaz para la indicación a tratar.

Por ejemplo, típicamente, una dosificación eficaz para inhibidores de HMG-CoA reductasa está en el intervalo de 0,01 a 100 mg/kg/día. En general, una dosificación de efecto para un modulador de PPAR está en el intervalo de 0,01 a 100 mg/kg/día.

Los compuestos de la presente invención se administran generalmente en forma de una composición farmacéutica que comprende al menos uno de los compuestos de esta invención junto con un vehículo, diluyente o excipiente farmacéuticamente aceptable como se describe a continuación. De esta forma, los compuestos de esta invención pueden administrarse individualmente o juntos en cualquier forma de dosificación convencional oral, rectal o transdérmica convencional.

Para la administración oral, una composición farmacéutica puede tomar la forma de soluciones, suspensiones, comprimidos, píldoras, cápsulas, polvos y similares. Se emplean comprimidos que contienen diversos excipientes tales como citrato sódico, carbonato cálcico y fosfato cálcico junto con diversos disgregantes tales como almidón y preferiblemente almidón de patata o tapioca y ciertos silicatos complejos, junto con agentes aglutinantes tales como polivinilpirrolidona, sacarosa, gelatina y goma arábiga. Adicionalmente, a menudo son muy útiles para formar comprimidos agentes lubricantes

tales como estearato de magnesio, lauril sulfato sódico y talco. También se emplean composiciones sólidas de un tipo similar como cargas en cápsulas de gelatina duras y blandas; los materiales preferidos en relación con esto incluyen lactosa o azúcar de la leche así como polietilenglicoles de alto peso molecular. Una formulación preferida es una solución o suspensión en un aceite, por ejemplo, un aceite vegetal, tal como aceite de oliva; triglicéridos tales como los comercializados con el nombre comercial Migylol™; o mono- o diglicéridos tales como los comercializados con el nombre comercial Capmul™, por ejemplo, en una cápsula de gelatina blanda. Se pueden añadir antioxidantes para evitar la degradación a largo plazo cuando sea apropiado. Cuando se deseen suspensiones acuosas y/o elixires para administración oral, los compuestos de esta invención pueden combinarse con diversos agentes edulcorantes, aromatizantes, colorantes, emulsionantes y/o de suspensión, así como diluyentes tales como agua, etanol, propilenglicol, glicerina y diversas combinaciones de los mismos.

En la Publicación Internacional WO 02/11710, que se incorpora como referencia en este documento, se describen composiciones farmacéuticas que comprenden una dispersión sólida amorfa de un inhibidor de la proteína de transferencia de éster de colesterol (CETP) y un polímero que aumenta la concentración. En la Publicación Internacional Nº WO 03/000295, que se incorpora como referencia en este documento, se describen formulaciones auto-emulsionantes de inhibidores de la proteína de transferencia de éster de colesterol (CETP). En la bibliografía se indican procedimientos para depositar pequeños cristales de fármaco en excipientes, tal como en J. Pharm. Pharmacol. 1987, 39:769-773, que se incorpora como referencia en este documento.

Para los fines de administración parenteral, se pueden emplear soluciones en aceite de sésamo o de cacahuete o en propilenglicol acuoso, así como soluciones acuosas estériles de las correspondientes sales solubles en agua. Tales soluciones

acuosas pueden tamponarse adecuadamente, si es necesario, y el diluyente líquido primero debe hacerse isotónico con suficiente solución salina o glucosa. Estas soluciones acuosas son especialmente adecuadas para propósitos de inyección intravenosa, intramuscular, subcutánea e intraperitoneal. En relación con esto, los medios acuosos estériles empleados se pueden obtener fácilmente por técnicas convencionales que conocen bien los especialistas en la técnica.

Para propósitos de administración transdérmica (por ejemplo, tópica), se preparan soluciones estériles diluidas, acuosas o parcialmente acuosas (normalmente con una concentración de aproximadamente 0,1% a 5%), por lo demás similares a las soluciones parenterales anteriores.

Los procedimientos para preparar diversas composiciones farmacéuticas con una cierta cantidad de ingrediente activo son conocidos o serán evidentes para los especialistas en la técnica en vista de esta descripción. Como ejemplos de procedimientos para preparar composiciones farmacéuticas, véase Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Las composiciones farmacéuticas de acuerdo con la invención pueden contener de un 0,1% a un 95% del compuesto o de los compuestos de esta invención, preferiblemente de un 1% a un 70%. En cualquier caso, la composición o formulación a administrar contendrá una cantidad de uno o más compuestos de acuerdo con la invención en una cantidad eficaz para tratar la enfermedad/trastorno del sujeto que se esté tratando, por ejemplo, aterosclerosis.

Como la presente invención tiene un aspecto que se refiere al tratamiento de las enfermedades/trastornos descritos en este documento con una combinación de ingredientes activos que pueden administrarse por separado, la invención también se refiere a la combinación de distintas composiciones farmacéuticas en forma de kit. El

kit comprende dos composiciones farmacéuticas distintas: un compuesto de la presente invención, un profármaco del mismo o una sal de tal compuesto o profármaco y un segundo compuesto como se ha descrito anteriormente. El kit comprende medios para contener las distintas composiciones, tal como un recipiente, un frasco dividido o un paquete laminado dividido. Típicamente, el kit comprende instrucciones para la administración de los distintos componentes. La forma de kit es particularmente ventajosa cuando los distintos componentes se administran preferiblemente en formas de dosificación diferentes (por ejemplo, oral y parenteral), se administran en distintos intervalos de dosificación o cuando el médico que la prescribe desea una valoración de los componentes individuales de la combinación.

Un ejemplo de tal kit es el denominado blister. Los blister son bien conocidos en la industria de envasados y se usan ampliamente para envasar formas de dosificación unitarias farmacéuticas (comprimidos, cápsulas y similares). Los blister generalmente constan de una lámina de material relativamente rígido cubierto con una capa de un material plástico preferiblemente transparente. Durante el proceso de envasado se forman cavidades en la capa de plástico. Las cavidades tienen el tamaño y la forma de los comprimidos o cápsulas a envasar. Después, los comprimidos o cápsulas se introducen en las cavidades y la lámina de material relativamente rígido se sella contra la capa de plástico por la cara de la capa opuesta a la dirección en la que se formaron las cavidades. Como resultado, los comprimidos o cápsulas quedan sellados en las cavidades entre la capa de plástico y la lámina. Preferiblemente, la resistencia de la lámina es tal que los comprimidos o cápsulas pueden retirarse del blister aplicando manualmente una presión en las cavidades, con lo que se forma una abertura en la lámina en el lugar de la cavidad. Entonces, el comprimido o cápsula puede retirarse a través de dicha abertura.

Puede ser deseable proporcionar una ayuda para recordar en el kit, por ejemplo, en forma de números próximos a los comprimidos o cápsulas que corresponden con los días del régimen en los que los comprimidos o cápsulas especificados de esta forma deben ingerirse. Otro ejemplo de tal ayuda para recordar es un calendario impreso en la tarjeta, por ejemplo como se indica a continuación "Primera Semana, Lunes, Martes, ... etc ... Segunda Semana, Lunes, Martes ... " etc. Otras variaciones de ayudas para recordar serán evidentes. Una "dosis diaria" puede ser un único comprimido o cápsula o varias píldoras o cápsulas para tomar en un día dado. Además, una dosis diaria de compuestos de la presente invención puede constar de un comprimido o cápsula, mientras que una dosis diaria del segundo compuesto puede constar de varios comprimidos o cápsulas y viceversa. La ayuda para recordar debe reflejar esto.

En otra realización específica de la invención se proporciona un dispensador diseñado para dispensar las dosis diarias de una en una en el orden de uso adecuado. Preferiblemente, el dispensador dispone de una ayuda para recordar, de forma que se facilite adicionalmente la aceptación del régimen. Un ejemplo de tal ayuda para recordar es un contador mecánico que indica el número de dosis diarias que se han dispensado. Otro ejemplo de tal ayuda para recordar es un microchip de memoria que funciona a pilas acoplado a una pantalla de cristal líquido, o señal audible, que, por ejemplo, muestra la fecha en la que se tomó la última dosis diaria y/o recuerda cuándo se debe tomar la siguiente dosis.

Los compuestos de esta invención solos o en combinación entre sí o con otros compuestos se administrarán generalmente en una formulación conveniente. Los siguientes ejemplos de formulación son sólo ilustrativos y no pretenden limitar el alcance de la presente invención.

En las formulaciones que se proporcionan a continuación, "ingrediente activo"

significa un compuesto de esta invención.

Formulación 1: Cápsulas de Gelatina

Se preparan cápsulas de gelatina dura usando los siguientes ingredientes:

Ingrediente	Cantidad (mg/cápsula)
Ingrediente activo	0,25-100
Almidón, NF	0-650
Polvo de almidón fluido	0-50
Silicona líquida 3,5 cm^2/s	0-15

Se prepara una formulación de comprimidos usando los siguientes ingredientes:

Formulación 2: Comprimidos

Ingrediente	Cantidad (mg/comprimido)
Ingrediente activo	0,25-100
Celulosa, microcristalina	200-650
Dióxido de silicio, de pirólisis	10-650
Ácido esteárico	5-15

Los componentes se mezclan y se comprimen para formar comprimidos

Como alternativa, se preparan comprimidos que contienen cada uno 0,25-100 mg de ingredientes activos como se indica a continuación:

Formulación 3: Comprimidos

Ingrediente	Cantidad (mg/comprimido)
Ingrediente activo	0,25-100
Almidón	45
Celulosa, microcristalina	35
Polivinilpirrolidona (solución al 10% en agua)	4
Carboximetilcelulosa sódica	4,5

Estearato de magnesio	0,5
Talco	1

Los ingredientes activos, el almidón y la celulosa se pasan a través de un tamiz de malla U.S. Nº 45 y se mezclan minuciosamente. La solución de polivinilpirrolidona se mezcla con los polvos resultantes que después se pasan a través de un tamiz de malla U.S. Nº 14. Los gránulos producidos de esta forma se secan a 50ºC-60ºC y se pasan a través de un tamiz de malla U.S. Nº 18. Después se añaden la carboximetilalmidón sódica, el estearato de magnesio y el talco pasados previamente a través de un tamiz de malla U.S. Nº 60 a los gránulos que, después de la mezcla, se comprimen en una máquina de formación de comprimidos para producir comprimidos.

Se preparan suspensiones que contienen cada una 0,25-100 mg de ingrediente activo por dosis de 5 ml como se indica a continuación:

Formulación 4: Suspensiones

Ingrediente	Cantidad (mg/5 ml)
Ingrediente activo	0,25-100 mg
Carboximetilcelulosa sódica	50 mg
Jarabe	1,25 mg
Solución de ácido benzoico	0,10 ml
Aroma	c.v.
Color	c.v.
Agua purificada hasta	5 ml

El ingrediente activo se pasa a través de un tamiz de malla U.S. Nº 45 y se mezcla con la carboximetilcelulosa sódica y el jarabe para formar una pasta uniforme. La solución de ácido benzoico, el aromatizante y el colorante se diluyen con un poco de agua y se añaden con agitación. Después se añade suficiente agua para producir el

volumen requerido.

Se prepara una solución para aerosol que contiene los siguientes ingredientes:

Formulación 5: Aerosol

Ingrediente	Cantidad (% en peso)
Ingrediente activo	0,25
Etanol	25,75
Propelente 22 (Clorodifluorometano)	70,00

El ingrediente activo se mezcla con etanol y la mezcla se añade a una porción del propelente 22, se enfría a 30ºC y se pasa a un dispositivo de llenado. Después se introduce la cantidad requerida en un recipiente de acero inoxidable y se diluye con el resto del propelente. Después se ajustan las válvulas al recipiente.

Los supositorios se preparan como se indica a continuación:

Formulación 6: Supositorios

Ingrediente	Cantidad (mg/supositorio)
Ingrediente activo	250
Glicéridos de ácidos grasos saturados	2.000

El ingrediente activo se pasa a través de un tamiz de malla U.S. Nº 60 y se suspende en los glicéridos de ácidos grasos saturados fundidos previamente usando el calor mínimo necesario. Después, la mezcla se vierte en un molde de supositorios con una capacidad nominal de 2 g y se deja enfriar.

Una formulación intravenosa se prepara como se indica a continuación:

Formulación 7: Solución Intravenosa

Ingrediente	Cantidad
Ingrediente activo disuelto en etanol al 1%	20 mg
Emulsión Intralipid™	1.000 ml

La solución de los ingredientes anteriores se administra por vía intravenosa a un paciente a una velocidad de aproximadamente 1 ml por minuto.

Se preparan cápsulas de gelatina blandas usando los siguientes ingredientes:

Formulación 8: Cápsulas de Gelatina Blanda con Formulación de Aceite

Ingrediente	Cantidad (mg/cápsula)
Ingrediente activo	10-500
Aceite de Oliva o Aceite Miglyol™	500-1.000

El ingrediente activo anterior también puede ser una combinación de agentes.

PROCEDIMIENTOS EXPERIMENTALES GENERALES

Los siguientes ejemplos se describen para proporcionar a los especialistas en la técnica una descripción de cómo se fabrican y se evalúan los compuestos, composiciones y procedimientos reivindicados en este documento, y pretenden servir como ejemplo de la invención y no pretender limitar el alcance de lo que los inventores consideran su invención. A menos que se indique otra cosa, el porcentaje es el porcentaje en peso dado el componente y el peso total de la composición, la temperatura está en °C o es la temperatura ambiente y la presión es la presión atmosférica o está cerca de ésta.

Los reactivos comerciales se utilizaron sin purificación adicional. Temperatura ambiente se refiere a 20-25°C. Todas las reacciones no acuosas se realizaron en una atmósfera de nitrógeno por conveniencia y para maximizar los rendimientos. La concentración al vacío significa que se usó un evaporador rotatorio. Los nombres de los compuestos de la invención se crearon con la versión Autonom 2.0 PC-batch de Beilstein Informationssysteme GmbH (ISBN 3-89536-976-4). Las estructuras químicas representadas sólo pueden ejemplificar la estructura general o isómeros limitados, y no incluye la estereoquímica específica que se indica en el nombre químico.

Los espectros de RMN se registraron en un espectrómetro de RMN Varian Unity 400 (Varian Co., Palo Alto, CA) a temperatura ambiente. Los desplazamientos químicos se expresan en partes por millón (□) en relación con un patrón externo (tetrametilsilano). Las formas de los picos se denotan como se indica a continuación: s, singlete; d, doblete; t, triplete; q, cuadruplete; m, multiplete, indicando el prefijo "a" una señal ensanchada. Los datos de la constante de acoplamiento (J) dados tienen un error máximo de ±0,41 Hz debido a la digitalización de los espectros adquiridos. Los espectros de masas se obtuvieron por (1) ionización química a presión atmosférica (APCI) alternando modo iónico positivo y negativo usando un Fisons Platform II Spectrometer o un Micromass MZD Spectrometer (Micromass, Manchester, UK) o (2) ionización por electronebulización alternando modo iónico positivo y negativo usando un Micromass MZD Spectrometer (Micromass, Manchester, UK) con un interfaz Gilson LC-MS (Gilson Instruments, Middleton, WI) o (3) un espectrómetro de masas QP-8000 (Shimadzu Corporation, Kyoto, Japón) en modo de control de ion positivo o negativo, utilizando ionización con electronebulización o ionización química a presión atmosférica. Cuando se describe la intensidad de los iones que contienen cloro o bromo, se observó la relación de intensidad esperada (aproximadamente 3:1 para iones que contienen ^{35}Cl /^{37}Cl y 1:1 para iones que contienen ^{79}Br/^{81}Br) y sólo se da la posición del ion de menor masa.

La cromatografía en columna se realizó con Gel de Sílice Baker (40 μm) (J.T. Baker, Phillipsburg, N.J.) o Gel de Sílice 60 (40-63 μm) (EM Sciences, Gibbstown, N.J.). La cromatografía ultrarrápida se realizó usando una columna Flash 12 o Flash 40 (Biotage, Dyar Corp., Charlottesville, VA). La purificación por HPLC preparativa se realizó en un sistema de HPLC preparativa Shimadzu 10A (Shimadzu Corporation, Kyoto, Japón) usando un automuestreador modelo SIL-10A y bombas de HPLC modelo

8A. La HPLC-MS preparativa se realizó en un sistema idéntico, modificado con un espectrómetro de masas QP-8000 funcionando en modo de control de ion positivo o negativo, utilizando ionización con electronebulizador o ionización química a presión atmosférica. La elución se realizó usando gradientes de agua/acetonitrilo que contenían un 0,1% de ácido fórmico o hidróxido de amonio como modificador. En modo ácido, las columnas típicas usadas incluyen Waters Symmetry C8, 5 µm 19x50 mm o 30x50mm, Waters XTerra C18, 5 µm, 50x50 (Waters Corp, Milford, MA) o Phenomenex Synergi Max-RP 4µm, 50x50 mm (Phenomenex Inc., Torrance, CA). En modo básico, se usaron las columnas Phenomenex Synergi Max-RP 4µm, 21,5x50 mm o 30x50 mm (Phenomenex Inc., Torrance, CA).

Las rotaciones ópticas se determinaron usando un Jasco P-1020 Polarimeter (Jasco Inc., Easton, MD).

La dimetilformamida, el tetrahidrofurano, el tolueno y el diclorometano eran de calidad anhidra y se proporcionaron por Aldrich Chemical Company (Milwaukee, WI). A menos que se especifique lo contrario, los reactivos se usaron como se obtuvieron a partir de fuentes comerciales. Los términos "concentrado" y "evaporado" se refieren a la retirada de disolvente a 1-200 mm de presión de mercurio en un evaporador rotatorio con una temperatura de baño de menos de 45ºC. La abreviatura "min" corresponde a "minutos" y "h" a "horas". La abreviatura "g" corresponde a gramos. La abreviatura "µl" corresponde a microlitros.

Preparación 1

Éster etílico del ácido (*R,S*)-2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Procedimiento 1)

A una solución de éster etílico del ácido (*R,S*)-4-amino-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (1294 g, 4,09 mmol preparado de acuerdo con el

procedimiento descrito en el documento WO 0140190) en ácido acético glacial (3882 ml) se le añadió una solución de nitrito sódico (582 g, 8,18 mol) en agua (1.618 ml), manteniendo una temperatura de 20 a 25°C. El disolvente se retiró al vacío, el residuo se disolvió en cloruro de metileno (2006 ml) y la solución se lavó con una solución saturada de hidrogenocarbonato sódico. EL disolvente se retiró por destilación a presión atmosférica y el residuo se disolvió en etanol anhidro (2688 ml) y se trató con hidróxido sódico acuoso (62,2 g, 1,55 mol). El disolvente se retiró al vacío, el residuo se disolvió en cloruro de metileno (2000 ml), se lavó con agua, se secó sobre sulfato de magnesio anhidro y se evaporó a sequedad al vacío para dar el compuesto del título en forma de un aceite (1219 g) que se usó sin purificación adicional en el siguiente procedimiento

Preparación 2

Éster etílico del ácido (*R,S*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*R,S*)-2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (1208 g, 3,81 mmol) en cloruro de metileno (4663 ml) se le añadió 2,2,6,6-tetrametil-1-piperidiniloxi (TEMPO), radical libre (6,1 g, 0,038 mol) y una solución de bromuro de potasio (45,8 g, 0,381 mol) disuelta en agua (191 ml). Una solución de hipoclorito sódico acuoso al 6% (7748 ml) que se había tamponado a pH 8,6 a 9,5 con hidrogenocarbonato sódico (78 g) se añadió lentamente de 0 a 5°C. La capa acuosa se lavó con cloruro de metileno (1208 ml). Las capas orgánicas combinadas se lavaron con ácido clorhídrico 1,4N (1493 ml) al que se le había añadido yoduro de potasio (12,8 g, 0,076 moles), después tiosulfato sódico acuoso (60,8 g, 0,381 mol) disuelto en agua (1208 ml) y finalmente agua (1691 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se evaporó a sequedad al vacío para dar el compuesto del título en forma de un aceite amarillo (1193 g).

^{1}H RMN (DMSO-d_6) □ 8,03 (m, 2H), 7,91 (dd, J =9,12, 2,49 Hz, 1H), 4,79 (m, 1H), 4,23 (q, J = 7,05 Hz, 2H), 3,25 (dd, J = 17,42, 5,81 Hz, 1H), 2,61 (dd, J = 17,42, 1,66 Hz, 1H), 1,42 (m, 2H), 1,25 (t, J = 7,05 Hz, 3H), 0,76 (t, J = 7,05 Hz, 3H).

Preparaciones 3 y 4

Éster etílico del ácido (*R*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (3) y éster etílico del ácido (*R*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (4)

El éster etílico del ácido (*RS*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico se resolvió por cromatografía quiral en un columna de 10 cm x 25 cm cargada con Chiralcel OD (Chiral Technologies Inc., Exton, PA). La cetona racémica (300 mg) en metanol (0,84 ml) se inyectó en columna y se eluyó con heptano:isopropanol 99:1 con un caudal de 275 ml/min par dar los compuestos del título:

Éster etílico del ácido (*R*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (3), tiempo de retención 7,82 min, $[\alpha]_D$ = -139,81° (c=0,438, cloroformo)

Éster etílico del ácido (*S*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (4), tiempo de retención 8,93 min, $[\alpha]_D$ = +139,7° (c=0,41, cloroformo)

Preparación 5

Éster etílico del ácido 4-hidrazono-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido 6,7.dimetoxi-2-metil-4-oxo-3,4-dihidro-2H-quinolin-1-carboxílico (1,00 g, 3,41 mmol, preparado de acuerdo con el procedimiento descrito en la Patente Alemana DE 2461050), hidrato de hidracina (330 µl, 6,80 mmol) y etanol (4,5 ml) se calentó en un vial cerrado con una pinza a 150°C durante 30 minutos en un horno microondas (Emrys Optimizer, Personal Chemistry,

Uppsala, Suecia). El disolvente se retiró al vacío, el residuo se disolvió en etanol (4,5 ml), se añadió hidrato de hidracina (330 µl, 6,80 mmol) y la solución se calentó como antes a 150ºC durante 30 minutos. El disolvente se evaporó al vacío para dar el compuesto del título en forma de un sólido amarillo pálido.

MS: 308,2 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,39 (s, 1H), 7,03 (s a, 1H), 5,21 (s, 2H), 5,03 (m, 1H), 4,27 (m, 1H), 4,15 (m, 1H), 3,88 (s, 3H), 3,85 (s, 3H), 2,61 (dd, J = 17, 5,81 Hz, 1H), 2,53 (dd, J = 17, 1,66 Hz, 1H), 1,28 (t, J = 7,4Hz, 3H), 1,08 (d, J = 6,64 Hz, 3H)..

Preparación 6

Éster etílico del ácido (*R*)-2-etil-4-hidrazono-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido (*R*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 3, 1,13 g, 3,58 mol), hidrato de hidracina (348 µl, 7,16 mmol) y etanol (10 ml) se calentó en un aparato Dean-Stark en condiciones que permitían la destilación lenta del disolvente. Después de 5 horas, se habían recogido aproximadamente 5 ml de destilado. La solución se diluyó con un volumen igual de tolueno y el disolvente se evaporó al vacío para dar un sólido verde pálido que se trituró y aclaró con un poco de hexano para dar el compuesto del título en forma de sólido casi incoloro (1,07 g).

MS: 330,2 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 8,23 (s, 1H), 7,62 (d a, J = 8,30 Hz, 1H), 7,46 (dd, J = 8,30, 1,66 Hz, 1H), 5,45 (s a, 2H), 4,82 (m, 1H), 4,28 (m, 1H), 4,24 (m, 1H), 2,64 (m, 2H), 1,36 (m, 2H), 1,31 (t, J = 7,47 Hz, 3H), 0,84 (t, J = 7,47 Hz, 3H).

Preparación 7

Éster etílico del ácido 4-diazo-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-

carboxílico

A una solución de éster etílico del ácido 4-hidrazono-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 5, 200 mg, 0,65 mmol) en éter dietílico (20 ml) se le añadió óxido de manganeso (IV) (400 mg, activado, ~85%, Aldrich Chemical Company, Milwaukee, WI). La suspensión se agitó a temperatura ambiente en una atmósfera de nitrógeno en la oscuridad durante 30 minutos y después el sólido se retiró por filtración a través de Celite® para dar el compuesto del título en forma de solución de color fucsia que se usó típicamente de forma inmediata.

Preparación 8

Éster etílico del ácido (*R*)-4-diazo-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*R*)-2-etil-4-hidrazono-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 6, 317 mg, 0,962 mmol) en éter dietílico (6 ml) se le añadió óxido de manganeso (IV) (1,1 g, activado, ~85%, Aldrich Chemical Company, Milwaukee, WI). La suspensión se agitó a temperatura ambiente en una atmósfera de nitrógeno en la oscuridad durante 1,5 horas y después el sólido se retiró por filtración a través de Celite®. El filtrado se diluyó con tolueno (15 ml) antes de evaporar a un volumen final de aproximadamente 10 ml (nunca a sequedad) para dar el compuesto del título en forma de solución de color fucsia que se usó típicamente de forma inmediata.

Preparaciones 9 y 10

Éster etílico del ácido (*R*)-4-cloro-2-etil-4-metoxicarbonocarbonil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (9) y éster etílico del ácido (*R*)-2-etil-4-metoxicarbonocarbonil-6-trifluorometil-2*H*-quinolin-1-carboxílico (10)

A una solución de éster etílico del ácido (*R*)-4-diazo-2-etil-6-trifluorometil-3,4-

dihidro-2*H*-quinolin-1-carboxílico (Preparación 8) preparado a partir de la Preparación 6 (317 mg, 0,962 mmol) en forma de solución en tolueno como se ha descrito anteriormente se le añadió N,N-diisopropiletilamina (335 µl, 1,92 mmol) seguido, gota a gota, de clorooxoacetato de metilo (0,962 mmol, 88,4 µl). La mezcla se dejó en agitación a temperatura ambiente en una atmósfera de nitrógeno. Se observó desprendimiento del de gas y el color fucsia cambió a amarillo-naranja en aproximadamente 10 minutos. La solución se diluyó con acetato de etilo, se lavó con una solución saturada de hidrogenocarbonato sódico y después con agua, se secó sobre sulfato sódico anhidro y se evaporó a sequedad. El residuo se cromatografió en sílice eluyendo con un gradiente de hexanos:acetato de etilo de 19:1 a 4:1 para dar los compuestos del título:

Éster etílico del ácido (*R*)-4-cloro-2-etil-4-metoxicarbonocarbonil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (9) (diastereoisómero que eluye antes, 82 mg)

MS: 422,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,72 (d, J = 9,13 Hz, 1H), 7,58 (m, 1H), 7,54 (s, 1H), 4,57 (m, 1H), 4,27 (m, 1H), 4,25 (m, 1H), 3,95 (s, 3H), 2,85 (dd, J = 14,11, 6,64 H, 1H), 2,77 (d, J = 14,11, 6,92 Hz, 1H), 1,61 (m, 1H), 1,52 (m, 1H), 1,30 (t, J = 7,47 Hz, 3H), 0,87 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*R*)-4-cloro2-etil-4-metoxicarbonocarbonil-6-trifluorometil-2*H*-quinolin-1-carboxílico (diastereoisómero que eluye en último lugar, 73 mg)

MS: 422,2 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,88 (s, 1H), 7,60 (m, 2H), 7,54 (s, 1H), 4,57 (m, 1H), 4,22 (m, 1H), 4,20 (m, 1H), 3,73 (s, 3H), 3,26 (dd, J = 13,8, 7,47 Hz), 2,23 (dd, J = 13,8, 6,75

Hz, 1H), 1,5 (m, 1H), 1,53 (m, 1H), 1,27 (t, J = 7,47 Hz, 3H), 0,89 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*R*)-2-etil-4-metoxicarbonocarbonil-6-trifluorometil-2*H*-quinolin-1-carboxílico, 133 mg

MS: 384,1 $[M+H]^-$ encontrado

^{1}H RMN ($CDCl_3$) □ 8,27 (s, 1H), 7,71 (d a, J = 8,30 Hz, 1H), 7,56 (dd, J = 8,30, 1,66 Hz, 1H), 7,20 (d, J = 6,64 Hz, 1H), 5,21 (m, 1H), 4,28 (m, 2H), 3,95 (s, 3H), 1,57 (m, 1H), 1,41 (m, 1H), 1,32 (t, J = 7,47 Hz, 3H), 0,91 (t, J = 7,47 Hz, 3H).

Preparación 11

Éster etílico del ácido 2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Procedimiento 2)

A una solución de éster etílico del ácido 2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,89 g, 2,83 mmol) en metanol (20 ml) se le añadió borohidruro sódico sólido (102 mg, 2,8 mmol). Después de 10 minutos se añadió acetona para inactivar la reacción y la mezcla se agitó durante 2 horas antes de evaporar el disolvente al vacío. El residuo se disolvió en cloruro de metileno y la solución se lavó con ácido clorhídrico 0,05N. La capa orgánica se secó sobre sulfato sódico anhidro, se diluyó con tolueno y se evaporó a sequedad para dar el compuesto del título en forma de una mezcla de diastereoisómeros que se utilizaron posteriormente sin separación.

MS: 318,0 $[M+H]^+$ encontrado

(isómero trans, secundario) ^{1}H RMN ($CDCl_3$) □ 7,80 (d, J = 8,30 Hz, 1H), 7,69 (s, 1H), 7,49 (dd, J = 8,30 Hz, 1,66 Hz, 1H), 4,86 (m, 1H), 4,58 (m, 1H), 4,25 (m, 2H), 2,16 (m, 2H), 1,60 (m, 1H), 1,50 (m, 1H), 1,32 (t, J = 7,47 Hz, 3H), 0,90 (t, J = 7,47 Hz, 3H).

MS: 318,0 $[M+H]^+$ encontrado

(isómero cis, principal) ^{1}H RMN ($CDCl_3$) □ 7,73 (s, 1H), 7,58 (d, J = 9,13 Hz,

1H), 7,50 (dd, J = 9,13, 1,66 Hz, 1H), 4,55 (m, 1H), 4,41 (m, 1H), 4,24 (m, 2H), 2,52 (ddd, J = 13,28, 7,47, 4,98 Hz, 1H), 1,67 (m, 1H), 1,60 (m, 1H), 1,48 (m, 1H), 1,30 (t, J = 7,47Hz, 3H), 0,85 (t, J = 7,47 Hz, 3H).

Preparación 12

Éster etílico del ácido 4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Procedimiento 1)

El producto de la preparación anterior (Preparación 11, 2,83 mmol) se disolvió en cloruro de metileno anhidro (30 ml), se enfrió a 0ºC y se añadió trietilamina (1,0 ml, 7,17 mmol) seguido de cloruro de metanosulfonilo (245 µl, 3,16 mmol). Después de 2 horas, se añadió otra alícuota de trietilamina (1,0 ml, 7,17 mmol), y la mezcla se agitó a temperatura ambiente durante 15 horas y después se lavó con agua que contenía ácido clorhídrico 2 N (10 ml). La capa orgánica se secó sobre sulfato sódico anhidro, se evaporó a sequedad y se purificó por cromatografía en sílice eluyendo con hexanos:acetona 25:1para dar el compuesto del título en forma de mezcla desigual de diastereoisómeros (590 mg) que se usó posteriormente sin separación.

Diastereosiómero 1 (principal)

MS: 336,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,69 (d, J = 8,29 Hz, 1H), 7,60 (s, 1H), 7,63 (d, J = 8,29 Hz, 1H), 5,12 (dd, J = 6,64, 4,98 Hz, 1H), 4,60 (m, 1H), 4,27 (m, 2H), 2,60 (ddd, J = 14,11, 6,64, 6,64 Hz, 1H), 2,13 (ddd, J = 14,11, 6,64, 4,98 Hz, 1H), 1,64 (m, 1H), 1,54 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0,89 (t, J = 7,47 Hz, 3H).

Diastereosiómero 2 (secundario)

MS: 336,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,82 (s, 1H), 7,68 (d, J = 8,30 Hz, 1H), 7,51 (dd, J = 8,30, 1,66 Hz, 1H), 5,08 (dd, J = 5,81 Hz, 1H), 4,55 (m, 1H), 4,25 (m, 2H), 2,71 (ddd, J =

14,11, 5,81 Hz, 1H), 2,18 (ddd, J = 14,11, 5,81, 5,81 Hz, 1H), 1,74 (m, 1H), 1,60 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0, 91 (t, J = 7,47 Hz, 3H).

Preparación 13

Éster etílico del ácido (*R,S*)-2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Procedimiento 3)

A una solución de éster etílico del ácido (*R*)-2-etil-4-oxo-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (1,1 g, 3,49 mmol) en tetrahidrofurano anhidro a 0ºC en una atmósfera de nitrógeno se le añadió triisobutilborohidruro de potasio (K-Selectride®, 1M en tetrahidrofurano, 8,0 ml, 8 mmol. Después de 1,5 horas, la mezcla se dejó calentar a temperatura ambiente, se agitó durante 16 horas y después se añadió un alícuota más de K-Selectride® (3,49 ml, 3,49 mmol). Después de 1,5 horas, el disolvente se retiró al vacío, el residuo se disolvió en acetato de etilo (50 ml) y esta solución se lavó con una solución de hidróxido sódico 2 N (20 ml) seguido de peróxido de hidrógeno (30%, 15 ml), se secó sobre sulfato de magnesio anhidro y se concentró hasta un bajo volumen. El residuo se recogió en acetonitrilo y se evaporó a sequedad (x 3) para retirar el agua residual para dar el compuesto del título (100%), idéntico al isómero *cis* del producto descrito anteriormente (Preparación 11).

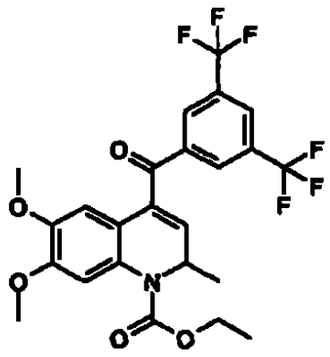
Preparación 14

Éster etílico del ácido (*R*)-4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Procedimiento 2)

Una solución de éster etílico del ácido (*R,S*)-2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 13, 1,1 g, 3,47 mmol) se disolvió en cloruro de tionilo (20 ml) a temperatura ambiente en una atmósfera de nitrógeno. Después de 1 hora, se añadió N,N-dimetilformamida (2 gotas) y la mezcla se dejó en agitación a temperatura ambiente durante 15 horas. El disolvente se retiró a presión

reducida y el residuo se cromatografió en sílice eluyendo con acetato:hexanos 50:1 para dar el compuesto del título en forma de un aceite amarillo (405 mg) con un espectro protónico RMN muy similar al obtenido para la Preparación 12 excepto que el componente principal y secundario de la mezcla estaban invertidos.

Ejemplo 1



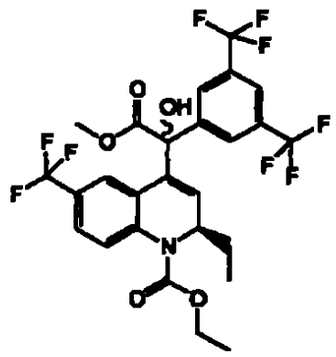
Éster etílico del ácido 4-(3,5-bis-trifluorometil)-benzoil)-6,7-dimetoxi-2-metil-2*H*-quinolin-1-carboxílico

Una solución de éster etílico del ácido 4-diazo-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 7, 0,65 mmol) preparada en forma de solución en éter dietílico como se ha descrito anteriormente se añadió a una solución de cloruro de 3,5-bistrifluorometilbenzoílo (180 mg, 0,65 mmol) y N,N-diisopropiletilamina (120 µl, 0,65 mmol) en éter dietílico (15 ml) y se dejó en agitación a temperatura ambiente en una atmósfera de nitrógeno en la oscuridad durante 15 horas. El disolvente se retiró al vacío y el residuo se cromatografió en sílice eluyendo con hexanos:acetato de etilo 3:1 para dar un producto parcialmente purificado que se purificó adicionalmente por cromatografía de fase inversa (gradiente lineal de acetonitrilo:agua, 55% a 100% de acetonitrilo, conteniendo ambas fases 0,1% de ácido fórmico) para dar el compuesto del título en forma de sólido amarillo limón (90 mg).

MS: 518,1 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 8,26 (s, 2H), 8,07 (s, 1H), 7,25 (s a, 1H), 7,0 4(s, 1H), 6,32 (d, J = 6,64 Hz, 1H), 5,31 (m, 1H), 4,33 (m, 1H), 4,23 (m, 1H), 3,91 (s, 3H), 3,80 (s, 3H), 1,33 (t, J = 7,47 Hz, 3H), 1,20 (d, J = 6,64 Hz, 3H).

Ejemplo 2



Éster etílico del ácido (*R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

Se preparó una solución de bromuro de 3,5-bis(trifluorometilfenil)magnesio por adición gota a gota de una solución de 3,5-bistrifluorometilbromobenceno (0,818 ml, 4,74 mmol) en tetrahidrofurano anhidro (0,7 ml) a una suspensión agitada de polvo de magnesio (116 mg, 4,74 mmol) en tetrahidrofurano anhidro (4,7 ml) a 35 °C. Después, la mezcla se calentó a reflujo durante 1 hora para dar una solución de color oscuro. Una parte de esta solución (1,5 ml) se añadió gota a gota a una solución de éster etílico del ácido (*R*)-2-etil-4-metoxicarbonocarbonil-6-trifluorometil-2*H*-quinolin-1-carboxílico (Preparación 10, 133 mg, 0,345 mmol) en tetrahidrofurano anhidro (4 ml) a -78°C. Después de 30 minutos, la mezcla se calentó a 0°C y se vertió en agua y se extrajo con acetato de etilo, añadiendo unas gotas de ácido clorhídrico acuoso 2 N para facilitar la separación de las capas. La capa orgánica se secó sobre sulfato sódico anhidro y se

evaporó a sequedad. Este procedimiento se repitió de forma exactamente similar usando éster etílico del ácido (*R*)-2-etil-4-metoxicarbonocarbonil-6-trifluorometil-2*H*-quinolin-1-carboxílico (Preparación 10, 235 mg, 0,609 mmol) en tetrahidrofurano anhidro (5 ml) y añadiendo la solución de bromuro de 3,5-bis(trifluorometilfenil)magnesio (2 ml). El producto bruto combinado se cromatografió en sílice eluyendo con un gradiente de acetato de etilo-hexanos de 5% a 30% para dar el compuesto del título en forma de una mezcla de diastereoisómeros (463 mg) que se usó posteriormente sin separación.

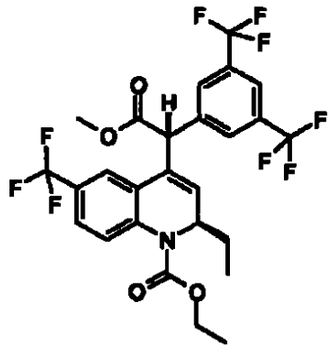
MS: 597,9 $[M+H]^-$ encontrado

Diastereoisómero 1: ^{1}H RMN ($CDCl_3$) □ 7,92 (s, 2H), 7,75 (s, 1H), 7,67 (s, 1H), 7,65 (d, J = 8,30 Hz, 1H), 7,34 (dd, J = 8,30, 1,66 Hz, 1H), 5,97 (d, J = 6,64 Hz, 1H), 5,04 (m, 1H), 4,53 (s, 1H), 4,27 (m, 2H), 3,87 (s, 3H), 1,47 (m, 1H), 1,35 (m, 1H), 1,28 (t, J = 7,47 Hz, 3H), 0,85 (d, J = 6,64 Hz, 3H).

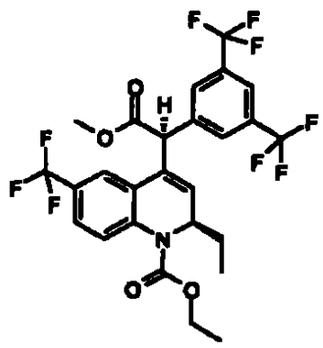
MS: 597,9 $[M-H]^-$

Diastereoisómero 2: ^{1}H RMN ($CDCl_3$) □ 8,16 (s, 2H), 7,90 (s, 1H), 7,65 (d, J = 8,30, 1H), 7,63 (s, 1H), 7,45 (dd, J = 8,30, 1, 66 Hz, 1H), 5,82 (d, J = 6,42 Hz, 1H), 4,96 (m, 1H), 4,34 (s, 1H), 4,27 (m, 2H), 3,78 (s, 3H), 1,47 (m, 1H), 1,35 (m, 1H), 1,33 (t, J = 7,47 Hz, 3H), 0,83 (d, J = 7,47 Hz, 3H).

Ejemplos 3 y 4



Éster etílico del ácido (*R,R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R,S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (ejemplo 2, 125 mg, 0,208 mmol) y 2,6-di-terc-butil-4-metilpiridina (256 mg, 1,248 mmol) en cloroformo (7ml) se le añadió cloruro de tionilo (30,4 µl, 0,417 mmol). Después de agitar durante 18 horas a temperatura ambiente, la mezcla se diluyó con cloruro de metileno, se lavó con agua y se secó sobre sulfato sódico anhidro. Después de retirar el disolvente al vacío, el residuo se cromatografió en sílice eluyendo con un gradiente de acetato de etilo-hexanos de 0% a 40% para dar éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-cloro-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico en forma de mezcla de tetrahidrofurano (2 ml) y ácido acético (2 ml). Se añadió polvo de cinc (200 mg, 3,05 mmol) seguido de ácido clorhídrico 2 N (1,5 ml). La suspensión se agitó a temperatura ambiente durante 3 horas y después se diluyó con cloruro de metileno y se lavó con agua. La capa orgánica se secó con sulfato sódico anhidro y se evaporó a sequedad al vacío. El residuo se cromatografió en sílice eluyendo con un gradiente de cloruro de metileno-hexanos de 60% a 80% para dar los

compuestos del título:

Diastereoisómero 1: 44 mg

MS: 584,0 $[M+H]^+$ encontrado

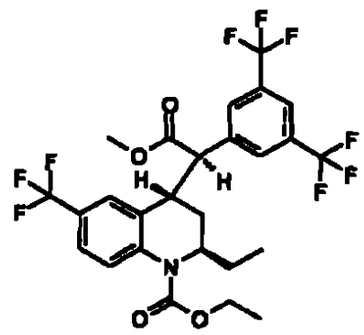
^{1}H RMN ($CDCl_3$) □ 7,79 (s, 1H), 7,76 (s, 2H), 7,74 (d, J = 8,30 Hz, 1H), 7,47 (d , J =8,30 Hz, 1H), 7,.41 (s, 1H), 6,02 (d, J = 6,64 Hz, 1H), 5,12 (s, 1H), 5,01 (m, 1H), 4,26 (m, 2H), 3,82 (s, 3H), 1,53 (m, 1H), 1,40 (m, 1H), 1,30 (t, J = 7,47 Hz, 3H), 0,87(d, J = 7,47 Hz, 3H)

Diastereoisómero 2: 16 mg

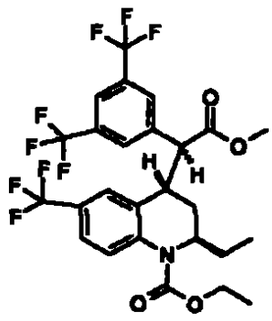
MS: 584,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,88 (s, 2H), 7,87 (s, 1H), 7,77 (d, J = 8,30 Hz, 1H), 7,49 (d, J = 8,30 Hz, 1H), 7,33 (s, 1H), 5,96 (d, J = 5,81 Hz, 1H), 5,07 (s, 1H), 5,00 (m, 1H), 4,29 (m, 2H), 3,74 (s, 3H), 1,47 (m, 1H), 1,36 (m, 1H), 1,34 (t, J =7,47 Hz, 3H), 0,84 (d, J = 7,47 Hz, 3H).

Ejemplos 5 y 6



Éster etílico del ácido (*RS.SR,RS*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*RS,SR,SR*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido 4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 12, 275 mg, 0,82 mmol) y éster metílico del ácido 3,5-bis(trifluorometilfenil)acético (286 mg, 1 mmol) en dimetilformamida anhidra (2 ml) se le añadió 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU, 100 mg). La mezcla se agitó a temperatura ambiente durante 24 horas y después a 50°C durante 15 horas. La mezcla se vertió en agua, se acidificó por adición de un poco de ácido clorhídrico 2 N y se extrajo con cloruro de metileno (x 3). El extracto se secó sobre sulfato sódico anhidro, se evaporó a sequedad y el residuo se purificó inicialmente por cromatografía de fase inversa y finalmente por cromatografía en sílice eluyendo con hexanos-acetato de etilo 6:1 para dar los compuestos del título.

Éster etílico del ácido (*RS,SR,RS*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (13,8 mg, diastereoisómero que eluye primero)

MS: 586,0 $[M+H]^+$ encontrado

^1H RMN ($CDCl_3$) □ 7,90 (s, 2H), 7,87 (s, 1H), 7,59 (d, J = 8,30 Hz, 1H), 7,62 (d, J = 8,30 Hz, 1H), 7,61 (s, 1H), 4,39 - 4,27 (m, 2H), 4,27 - 4,18 (m, 1H), 3,78 (d, J = 11,61 Hz, 1H), 3,59 (m, 1H), 3,48 (s, 3H), 1,76 (ddd, J = 14,10, 8,30, 3,30 Hz, 1H),

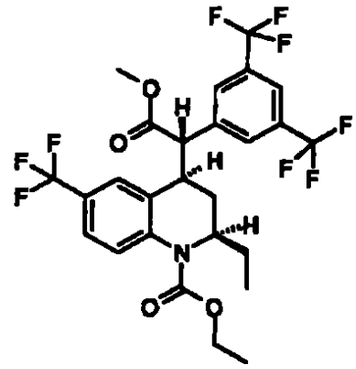
1,61-1,55 (m, 1H), 1,57-1,50 (m, 1H), 1,48-1,40 (m, 1H), 1,35 (t, J = 7,47 Hz, 3H), 0,73 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*RS,SR,SR*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

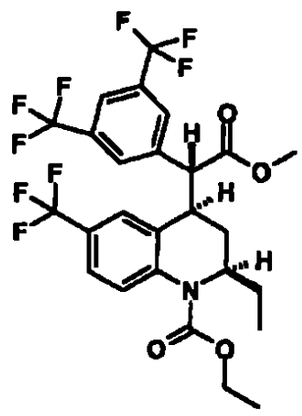
MS: 586,0 $[M+H]^+$ encontrado

^1H RMN ($CDCl_3$) □ 7,66 (s, 1H), 7,42 (s, J = 8,30 Hz, 1H), 7,40 (s, 2H), 7,33 (dd, J = 8,30 , 1,66 Hz, 1H), 6,47 (d, J = 1,66 Hz, 1H), 4,55-4,47 (m, 1H), 4,34 (m, 1H), 4,32 (m, 1H), 3,83 (d, J = 11,61 Hz, 1H), 3,80 (s, 3H), 3,43 (ddd, J = 11,61, 4,98, 2,49 Hz, 1H), 2,44 (ddd, J = 14,11, 8,30, 2,49 Hz, 1H), 1,81 (ddd, J = 14,10, 8,30, 4, 98 Hz, 1H), 1,67 (m, 1H), 1,51 (m, 1H), 1,33 (t, J = 7,47 Hz, 3H), 0,85 (t, J = 7,47 Hz, 3H).

Ejemplos 7 y 8



Éster etílico del ácido (*RS,RS,SR*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*2S,RS,SR*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido (*RS,RS*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico y éster etílico del ácido (*RS,SR*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (preparado con un procedimiento exactamente similar al descrito para los Ejemplos 3 y 4 con la excepción de que se usó material de partida racémico y la mezcla de los diastereoisómeros producida no se separó) (20 mg, 0,0342 mmol) en etanol (5 ml) que contenía hidróxido de paladio (20% en carbono, 20 mg) se hidrogenó en un agitador Parr (Parr Instrument Company, Moline, Illionis) a 40 psi durante 5 horas. El catalizador se retiró por filtración a través de Celite y el disolvente se retiró al vacío. El residuo se cromatografió en sílice eluyendo con un gradiente de acetato de etilo - hexanos de 0% a 10% para dar los compuestos del título.

Éster etílico del ácido (*RS,RS,SR*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (diastereoisómero que eluye en primer lugar, 8 mg)

MS: 586,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,89 (s, 1H), 7,88 (s, 2H), 7,53 (m, 2H), 7,39 (s, 1H), 4,55 -

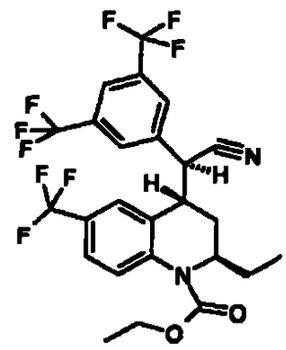
4,47 (m, 1H), 4,34-4,24 (m, 2H), 4,24-4,18 (m, 1H), 4,03 (d, J = 11,62 Hz, 1H), 3,77 (s, 3H), 3,38 (m, 1H), 1,75 (m, 1H), 1,49 (m, 1H), 1,38 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0,96 (m, 1H) 0,71 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*RS,RS,RS*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (diastereoisómero que eluye en segundo lugar, 5 mg)

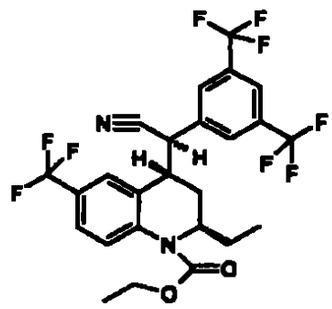
MS: 586,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,93 (s, 2H), 7,84 (s, 1H), 7,53 (d, J = 8,29 Hz, 1H), 7,43 (dd, J = 8,29 Hz, 1H), 7,07 (s, 1H), 4,42 (m, 1H), 4,27 (d, J = 9.96 Hz, 1H), 4,26 (m, 2H), 4,32 (m, 1H), 3,76 (s, 3H), 3,28 (m, 1H), 2,36 (m, 1H), 1,65 (m, 1H), 1,62 (m, 1H), 1,45 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0,84 (t, J = 7,47 Hz, 3H).

Ejemplos 9 y 10



Éster etílico del ácido (*R,S,S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R,S,R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se añadió hidruro sódico (dispersión al 60% en aceite mineral, 34 mg, 0,85 mmol) a una solución de 3,5-bis(trifluorometilfenil)acetonitrilo (212 mg, 0,84 mmol) en dimetilformamida anhidra (1,5 ml). Después de agitar en una atmósfera de nitrógeno durante 30 minutos a temperatura ambiente se añadió una solución de éster etílico del ácido (*R*)-4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 14, 188 mg, 0,56 mmol) en dimetilformamida anhidra (2 ml). La mezcla se agitó a temperatura ambiente durante 16 horas y después se vertió en agua (20 ml) y se extrajo con éter dietílico (3x20 ml). El extracto se secó sobre sulfato sódico anhidro y el disolvente se retiró al vacío. Este material se purificó por cromatografía en gel de sílice eluyendo inicialmente con acetato de etilo - hexanos (1:19) para obtener un diastereoisómero del compuesto deseado en forma impura que se purificó adicionalmente por cromatografía de fase inversa para obtener el compuesto del título del Ejemplo 9 en forma de aceite transparente (69 mg). La elución posterior de la columna de sílice con acetato de etilo - hexanos (1:4) proporcionó el compuesto del título del Ejemplo 10 en forma de aceite amarillo (54 mg).

Éster etílico del ácido (*R,S,S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 553,0 $[M+H]^+$ encontrado

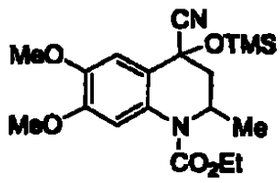
^{1}H RMN ($CDCl_3$) □ 7,80 (s, 1H), 7,60 (d, J = 8,30 Hz, 1H), 7,49 (dd, J = 8,30, 1,66 Hz, 1H), 7,40 (s, 2H), 6,60 (d, J = 1,66 Hz, 1H), 4,59 (m, 1H), 4,33 (m, 2H), 4,6 (d, J = 9,96, 1H), 3,20 (m, 1H), 2,78 (m, 1H), 1,89 (m, 1H), 1,65 (m, 1H), 1,53 (m, 1H), 1,34 (t, J = 7,47 Hz, 3H), 0,96 (m, 1H), 0,88 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*R,S,R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 553,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,89 (s, 1H), 7,62 (s, 2H), 7,62 (d, J = 8,30 Hz, 1H), 7,55 (d, J = 8,30Hz, 1H), 7,38 (s 1H), 4,41 (m, 1H), 4,24 (m, 2H), 4,16 (m, 1H), 4,15 (d, J = 8,30 Hz, 1H), 3,48 (m, 1H), 2,01 (m, 1H), 1,95 (m, 1H), 1,48 (m, 1H), 1,41 (m, 1H), 1,29 (t, J = 7,47 Hz, 3H), 0,77 (t, J = 7,47 Hz, 3H).

Preparación 15



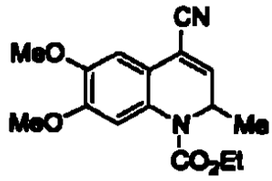
Éster etílico del ácido [(*R, R*),(*S, S*)] y [(*R, S*),(*S, R*)]-4-ciano-6,7-dimetoxi-2-metil-4-trimetilsilaniloxi-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se añadieron éster etílico del ácido [(*RS*)]-6,7-dimetoxi-2-metil-4-oxo-3,4-dihidro-2*H*-quinolin-1-carboxílico (8,02 g, 27,3 mmol, 1 eq) y yoduro de cinc (0,43 g, 1,37 mmol, 0,05 eq) a una matraz seco de fondo redondo equipado con una barra de agitación magnética y un condensador de reflujo en una atmósfera de nitrógeno. Se añadió tolueno (20 ml) al matraz seguido de cianuro de trimetilsililo (4, 40 ml, 33,0 mmol, 1,2 eq). La reacción se calentó a 80°C. Después de 5 horas, la mezcla de reacción

se concentró a sequedad para producir los compuestos del título (10,7 g, 27,2 mmol, rendimiento del 100%) que se usaron sin purificación adicional.

LCMS (ESI+): 393 (MH+)

Preparación 16



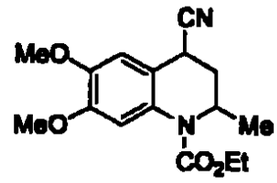
Éster etílico del ácido (*R,S*)-4-ciano-6,7-dimetoxi-2-metil-2*H*-quinolin-1-carboxílico

El éster etílico del ácido [(*R,R*),(*S,S*)] y [(*R,S*),(*S,R*)]-4-ciano-6,7-dimetoxi-2-metil-4-trimetilsilaniloxi-3,4-dihidro-2*H*-quinolin-1-carboxílico (10,7 g, 27,37 mmol) se introdujo en un matraz de100 ml de fondo redondo y se disolvió en etanol (25 ml). Se añadió a la mezcla ácido clorhídrico en dioxano (21,0 ml de una solución 4,0 M). Después de 12 horas a temperatura ambiente, la mezcla de reacción se concentró, se inactivó con una solución saturada de hidrogenocarbonato sódico y se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron. La cromatografía ultrarrápida eluyendo con hexanos/acetato de etilo 80/20 produjo los compuestos del título (5,49 g, 18,1 mmol, rendimiento del 67%).

LCMS (ESI+): 303 (MH+)

^{1}H RMN ($CDCl_3$) □ 1,13 (d, 3H), 1,33 (t, 3H), 3,90 (s, 3H), 3,92 (s, 3H), 4,30 (m, 2H); 5,25 (m, 1H), 6,65 (d, 1H), 6,91 (s, 1H), 7,24 (s a, 1H).

Preparaciones 17 y 18



Éster etílico del ácido [(*R*,*S*),(*S*,*R*)] y [(*R*,*R*),(*S*,*S*)]-4-ciano-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se introdujo éster etílico del ácido (*RS*)-4-ciano-6,7-dimetoxi-2-metil-2*H*-quinolin-1-carboxílico (4,99 g, 16,5 mmol) en un matraz de fondo redondo equipado con un barra de agitación magnética, se disolvió en 47 ml de etanol y se combinó con borohidruro sódico (3,18 g, 84,3 mmol, 5,1 eq). Después de 45 minutos de calentar a reflujo, la mezcla se concentró a sequedad, se inactivó con agua y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron y se concentraron para producir los compuestos del título (4,91 g, 16,1 mmol, rendimiento del 98%).

isómero *cis*:

LCMS (ESI+): 305 (MH+)

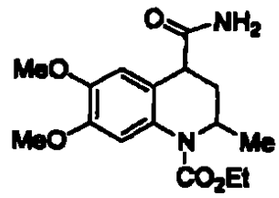
(*R*, *S*) y (*S*, *R*) ^{1}H RMN ($CDCl_3$) □ 1,23 (d, 3H), 1,29 (t, 3H), 1,78 (m, 1H), 2,65 (m, 1H), 3,74 (m, 1H), 3,86 (s, 3H), 3,90 (s, 3H), 4,22 (m, 2H), 4,61 (m, 1H), 6,92 (s, 1H), 7,10 (s, 1H).

isómero *trans*:

LCMS (ESI+): 305 (MH+)

(*R*, *R*) y (*S*, *S*) ^{1}H RMN ($CDCl_3$) □ 1,16 (d, 3H), 1,32 (t, 3H), 2,03 (m, 1H), 2,42 (m, 1H), 3,87 (s, 3H), 3,88 (s, 3H), 3,94 (m, 1H), 4,26 (m, 2H), 4,86 (m, 1H), 6,77 (s, 1H), 7,30 (s, 1H).

Preparaciones 19 y 20



Éster etílico del ácido [(*R*,*S*),(*S*,*R*)] y [(*R*,*R*),(*S*,*S*)]-4-carbamoil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se disolvió éster etílico del ácido [(*R*,*S*),(*S*,*R*)] y [(*R*,*R*),(*S*,*S*)]-4-ciano-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico(2,22 g, 7,32 mmol, 1 eq) en ácido sulfúrico concentrado (12 ml) y agua (0,66 ml, 36,6 mmol, 5 eq). Después de 12 horas a temperatura ambiente, la reacción se inactivó con bicarbonato sólido, se disolvió en agua y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico anhidro, se filtraron y se concentraron para proporcionar los compuestos del título (2,25 g, 6,98 mmol, rendimiento del 95%).

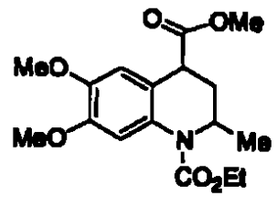
LCMS (ESI+): 323 (MH+)

[(*R*, *S*) y (*S*, *R*)]: ^{1}H RMN ($CDCl_3$) □ 1,20 (d, 3H), 1,30 (t, 3H), 1,89 (m, 1H), 2,41 (m, 1H), 3,37 (m, 1H), 3,84 (s, 3H), 3,86 (s, 3H), 4,22 (m, 2H), 4,55 (m, 1H), 5,70 (s, 1H), 5,80 (s, 1H), 6,70 (s, 1H), 7,21 (s, 1H).

LCMS (ESI+): 323 (MH+)

[(*R*, *R*) y (*S*, *S*)]: ^{1}H RMN ($CDCl_3$) □ 1,17 (d, 3H), 1,30 (t, 3H), 1,74 (m, 1H), 2,67 (m, 1H), 3,55 (m, 1H), 3,86 (s, 3H), 3,87 (s, 3H), 4,21 (m, 2H), 4,58 (m, 1H), 5,36 (s, 1H), 5,49 (s, 1H), 6,65 (s, 2H), 7,15 (s, 1H).

Preparaciones 21 y 22



Éster 4-metílico, éster etílico del ácido [(*R,S*),(*S,R*)] y [(*R,R*),(*S,S*)]- 6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

Se introdujo éster etílico del ácido [(*R,S*),(*S,R*)] y [(*R,R*),(*S,S*)]-4-carbamoil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (2,24 g, 6,95 mmol, 1 eq) en un matraz de 100 ml de fondo redondo equipado con una barra de agitación y se disolvió en cloruro de metileno (56,5 ml). Se añadió tetrafluoroborato de trimetiloxonio (1,29 g, 8,76 mmol, 1,26 eq) a la solución seguido de 12,2 ml más de cloruro de metileno. Después de 12 horas a temperatura ambiente la mezcla de reacción se concentró a sequedad y se usó sin purificación adicional. El producto (2,84 g, 6,95 mmol, 1 eq) se disolvió en agua (20 ml) y se agitó durante varias horas a temperatura ambiente. La mezcla se saturó con una solución de cloruro sódico, se extrajo 3 veces con acetato de etilo, se secó sobre sulfato sódico, se filtró y se concentró a sequedad. La cromatografía ultrarrápida eluyendo con hexanos/acetato de etilo 80/20 proporcionó los compuestos del título (1,65 g, 4,88 mmol, rendimiento del 70%).

LCMS (ESI+): 338 (MH+)

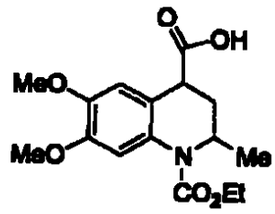
[(*R, S*) y (*S, R*)]: ^{1}H RMN ($CDCl_3$) □ 1,17 (d, 3H), 1,29 (t, 3H), 1,81 (m, 1H), 2,46 (m, 1H), 3,56 (m, 1H), 3,81 (s, 3H), 3,83 (s, 3H), 3,85 (s, 3H), 4,21 (m, 2H), 4,55 (m, 1H), 6,60 (s, 1H), 7,11 (s, 1H).

LCMS (ESI+): 338 (MH+)

[(*R, R*) y (*S, S*)]: ^{1}H RMN ($CDCl_3$) □ 1,13 (d, 3H), 1,29 (t, 3H), 1,78 (m, 1H), 2,54 (m, 1H), 3,67 (s, 3H), 3,71 (m, 1H), 3,84 (s, 3H), 3,85 (s, 3H), 4,21 (m, 2H), 4,74

(m, 1H), 6,66 (s, 1H), 7,13 (s, 1H).

Preparaciones 23 y 24



Éster 4-metílico, éster etílico del ácido [(*R*,*S*),(*S*,*R*)] y [(*R*,*R*),(*S*,*S*)]- 6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

Se disolvió éster etílico del ácido [(*R*,*S*),(*S*,*R*)] y [(*R*,*R*),(*S*,*S*)]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (0,62 g, 1,73 mmol, 1 eq) en dioxano (12 ml) y agua (12 ml) en un matraz con fondo redondo con una barra de agitación magnética. Se añadió hidróxido sódico (0,13 g, 3,48 mmol, 2 eq) y se agitó a temperatura ambiente. Después de 12 horas, la mezcla de reacción se concentró y se repartió entre hidróxido sódico acuoso 1,0 N y éter dietílico. La capa acuosa se recogió, se acidificó con ácido clorhídrico concentrado y se extrajo con éter. La capa orgánica se recogió, se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar los compuestos del título (0,536 g, 1,65 mmol, rendimiento del 90%) en forma de una mezcla de diastereoisómeros.

LCMS (ESI+): 324 (MH+)

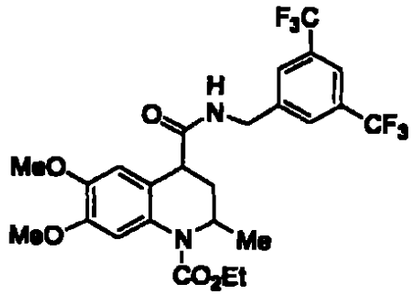
[(*R*, *S*) y (*S*, *R*)]: ^{1}H RMN ($CDCl_3$) □ 1,18 (d, 1H), 1,30 (t, 3H), 1,89 (m, 1H), 2,48 (m, 1H), 3,61 (m, 1H), 3,84 (s, 2H), 3,85 (s, 3H), 4,21 (m, 2H), 4,60 (m,1H), 6,75 (s, 1H), 7,15 (s, 1H).

LCMS (ESI+): 324 (MH+)

[(*R*, *R*) y (*S*, *S*)]: ^{1}H RMN ($CDCl_3$) □ 1,14 (d, 3H), 1,29 (t, 3H), 1,83 (m, 1H), 2,56 (m, 1H), 3,74 (m, 1H), 3,85 (s, 6H), 4,21 (m, 2H), 4,76 (m, 1H), 6,70 (s, 1H), 7,14

(s, 1H).

Ejemplos 11 y 12



Éster etílico del ácido [(*R,S*),(*S,R*)] y [(*R,R*),(*S,S*)]-4-(3,5-bis-trifluorometil-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se introdujo éster 1-etílico del ácido [(*R,S*),(*S,R*)] y [(*R,R*),(*S,S*)]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (0,229 g, 0,710 mmol) en un matraz de 25 ml de fondo redondo equipado con una barra de agitación. Se añadió cloruro de metileno (7,0 ml) seguido de la adición de 3,5-bis(trifluorometil)bencilamina (0,519 g, 2,14 mmol, 3,0 eq). A esta reacción, se le añadieron hidrato de 1-hidroxibenzotriazol (0,022 g, 0,146 mmol, 0,2 eq) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,232 g, 1,21 mmol, 1,7 eq). La mezcla de reacción se agitó a temperatura ambiente. Después de 12 horas, la reacción se inactivó con agua y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron y se concentraron para proporcionar los compuestos del título (0,1225 g, 0,223 mmol, rendimiento del 58%) en forma de una mezcla de diastereoisómeros.

LCMS (ESI+): 549 (MH+)

^{1}H RMN [(*R, S*) y (*S, R*)] y [(*R, R*) y (*S, S*)] ($CDCl_3$) □ 1,16 (d, 3H), 1,24 (t, 3H), 1,80 (m, 1H), 2,66 (m, 1H), 3,64 (m, 1H), 3,81 (s, 3H), 3,86 (s, 3H), 4,11 (m, 2H), 4,29

(m, 1H), 4,56 (m, 2H), 4,70 (m, 2H), 6,05 (m, 1H), 6,40 (m, 1H), 6,65 (s, 1H), 6,60 (s, 1H), 7,13 (s, 1H), 7,66 (s, 2H), 7,75 (s, 1H), 7,80 (s, 1H). LCMS (ESI+): 549 (MH+)

Preparaciones 25 y 26

Éster etílico del ácido [(*R,S*),(*S,R*)] y [(*R,R*),(*S,S*)]- 6,7-dimetoxi-4-(metoximetil-carbamoil)-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se disolvió éster 1-etílico del ácido [(*R,S*),(*S,R*)] y [(*R,R*),(*S,S*)]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (0,536 g, 1,55 mmol) en un matraz de 25 ml con fondo redondo equipado con una barra de agitación y se disolvió en cloruro de metileno (10 ml). La mezcla de reacción se enfrió a 0°C y se añadió di-*iso*-propiletilamina (0,18 g, 2,0 mmol, 1,3 eq) seguido de la adición de N,O-dimetilhidroxilamina (1,1 eq), 4-dimetilaminopiridina (0,1 eq) y clorhidrato 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1,2 eq). La mezcla de reacción se agitó a temperatura ambiente. Después de 12 horas, la mezcla de reacción se inactivó con agua y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron, se filtraron y se concentraron para proporcionar los compuestos del título (0,56 g, 1,52 mmol, rendimiento del 98%) que se usaron sin purificación adicional.

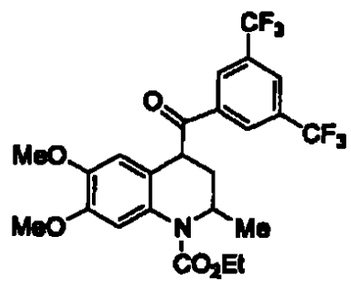
LCMS (ESI+): 367 (MH+)

[(*R, R*) y (*S, S*)]: ^{1}H RMN ($CDCl_3$) □ 1,10 (d, 3H), 1,28 (t, 3H), 1,83 (m, 1H), 2,41 (m, 1H), 3,16 (s, 3H), 3,38 (s, 3H), 3,80 (s, 3H), 3,82 (s, 3H), 4,06 (m, 1H), 4,21 (m, 2H), 4,84 (m, 1H), 6,55 (s, 1H), 7,16 (s, 1H).

LCMS (ESI+): 367 (MH+)

[(*R, S*) y (*S, R*)]: ^{1}H RMN ($CDCl_3$) □ 1,32 (d, 3H), 1,65 (t, 3H), 1,75 (m, 1H), 2,39 (m, 1H), 3,16 (s, 3H), 3,35 (s, 3H), 3,80 (s, 3H), 3,82 (s, 3H), 4,06 (m, 1H), 4,21 (m, 2H), 4,84 (m, 1H), 6,45 (s, 1H), 7,05 (s, 1H).

Ejemplos 13 y 14



Éster etílico del ácido [(*R*,*S*),(*S*,*R*)] y [(*R*,*R*),(*S*,*S*)]-4-(3,5-bis-trifluorometil-benzoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se disolvió éster 1-etílico del ácido [(*R*,*S*),(*S*,*R*)] y [(*R*,*R*),(*S*,*S*)]-6,7-dimetoxi-(4-metoxi-metil-carbamoil)-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,56 g, 1,45 mmol, 1 eq) en tetrahidrofurano (12 ml) en un matraz de fondo redondo equipado con una barra de agitación magnética. La reacción se enfrió a 0°C, se añadió gota a gota bromuro de 3,5-bis(trifluorometil)fenil magnesio (13,6 ml de una solución 0,5M) y la mezcla de reacción se agitó a temperatura ambiente. Después de 12 horas, la mezcla de reacción se inactivo con cloruro de amoniaco acuoso, posteriormente se saturó con NaCl y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron y se concentraron a sequedad. La cromatografía ultrarrápida eluyendo con 90/10 hexanos/acetato de etilo proporcionó los compuestos del título (0,556 g, 1,07 mmol, rendimiento del 73%).

LCMS (ESI+): 520 (MH+)

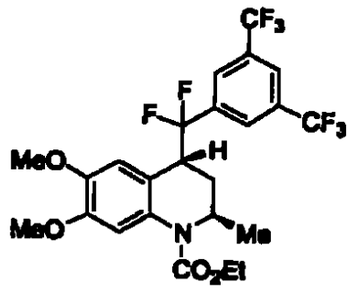
[(*R*, *S*) y (*S*, *R*)]: ^{1}H RMN ($CDCl_3$) □ 1,24 (d, 3H9, 1,35 (t, 3H), 1,81 (m, 1H), 2,52 (m, 1H), 3,63 (s, 3H), 3,88 (s, 3H), 4,29 (m, 2H), 4,42 (m, 1H), 4,57 (m, 1H), 6,21 (s, 1H), 7,15 (s, 1H), 8,13 (s, 1H), 8,45 (s, 2H).

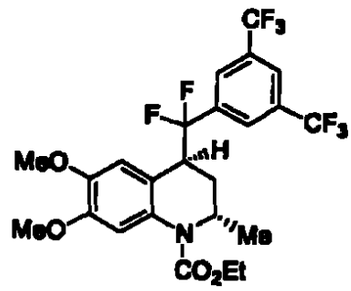
LCMS (ESI+): 520 (MH+)

[(*R*, *R*) y (*S*, *S*)]: ^{1}H RMN ($CDCl_3$) □ 1,18 (d, 3H), 1,28 (t, 3H), 1,88 (m, 1H), 2,67 (m, 1H), 3,79 (s, 3H), 3,84 (s, 3H9, 4,21 (m, 2H), 4,45 (t, 1H), 4,88 (m, 1H), 6,59

(s, 1H), 7,07 (s, 1H), 7,97 (s, 1H), 8,25 (s, 2H).

Ejemplo 15





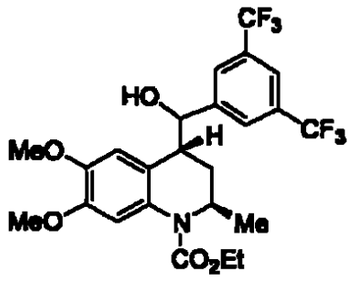
Éster etílico del ácido [(*R,R*),(*S,S*)]-4-(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-metil-5,6-dimetoxi-3,4-dihidro-2*H*-quinolin-1-carboxílico

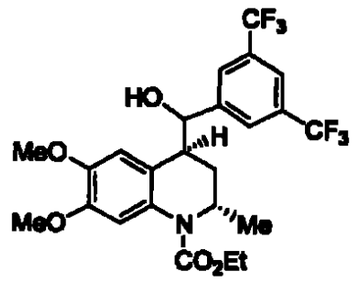
Se disolvió éster etílico del ácido [(*R,R*),(*S,S*)]-4-(3,5-bis-trifluorometil-benzoil)-2-metil-6,7-dimetoxi-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,062 g, 0,120 mmol) en cloruro de metileno (0,25 ml) en un vial equipado con una barra de agitación magnética. Se añadió trifluoruro de [bis(2-metoxietil)amino]azufre (0,22 ml, 1,20 mmol, 10 eq) a esta solución y la mezcla de reacción se agitó a temperatura ambiente. Después de 12 horas, la mezcla de reacción se inactivó con una solución de cloruro de amonio acuoso, y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron, se concentraron y se purificaron por cromatografía en sílice eluyendo con 90/10 hexanos/acetato de etilo proporcionó los compuestos del título (0,045 g, 0,08 mmol, rendimiento del 66%).

LCMS (ESI+): 542 (MH+)

[(*R, S*) y (*S, R*)]: ^{1}H RMN ($CDCl_3$) □1,10 (d, 3H), 1,22 (t, 3H), 1,95 (m, 1H), 2,45 (m, 1H), 3,55 (m, 1H), 3,75 (s, 3H), 3,87 (s, 3H9, 4,00 (m, 1H), 4,19 (m, 1H), 4,60 (m,1H), 6,45 (s, 1H), 6,99 (s, 1H), 7,6 (s, 2H), 7,9 (s, 1H).

Ejemplos 16 y 17





Éster etílico del ácido [(*R, R, R*),(*S, S, S*)] y [(*R, R, S*),(*S, S, R*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se introdujo éster etílico del ácido [(*R,R*),(*S,S*)]-4-(3,5-bis-trifluorometil-benzoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,302 g, 0,58 mmol, 1 eq) en un matraz de fondo redondo equipado con una barra de agitación magnética. Se añadió metanol (12 ml) seguido de la adición de borohidruro sódico (0,131 g, 3,48 mmol, 6 eq) a temperatura ambiente. Después de 1 hora, la mezcla de reacción se inactivó con una solución de salmuera, se extrajo 3 veces con acetato de etilo y se secó sobre sulfato sódico. El material se purificó por cromatografía ultrarrápida eluyendo con 75/25 hexanos/acetato de etilo para proporcionar los compuestos del título (0,271 g, 0,52 mmol, rendimiento del 89%).

Diastereoisómero 1 (rendimiento del 29%)

LCMS (ESI+): 522 (MH+).

^{1}H RMN ($CDCl_3$): □ 1,12 (d, 3H), 1,29 (t, 3H), 1,39 (m, 1H), 2,52 (m, 1H), 2,81 (s a, 1H), 2,94 (m, 1H), 3,65 (s, 4H), 3,83 (s, 3H), 4,21 (m, 2H), 4,67 (m, 1H), 5,04 (d, 1H), 6,18 (s, 1H), 7,02 (s, 1H), 7,64 (s, 2H), 7,72 (s, 1H).

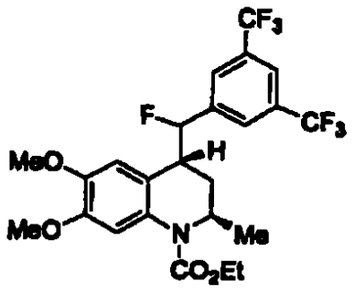
Diastereoisómero 2 (rendimiento del 60%)

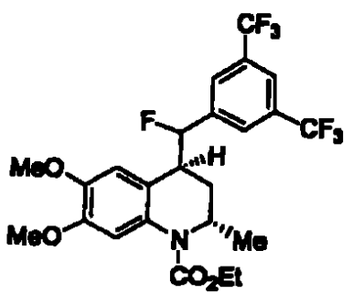
LCMS (ESI+): 522 (MH+)

^{1}H RMN ($CDCl_3$): □ 1,14 (d, 3H), 1,34 (t, 3H), 1,56 (m, 1H), 2,97 (m, 1H), 3,87

(s, 3H), 3,88 (s, 3H), 4,26 (m, 2H), 4,49 (m, 1H), 4,77 (d, 1H), 6,70 (s, 1H), 7,09 (s, 1H), 7,84 (s, 3H).

Ejemplos 18 y 19





Éster etílico del ácido [(*R, R, R*),(*S, S, S*)] y [(*R, R, S*),(*S, S, R*)]-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

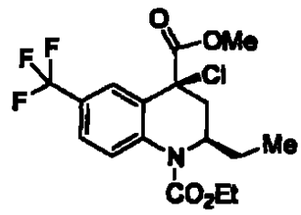
Se introdujo éter etílico del ácido [(*R, R, R*),(*S, S, S*)] y [(*R, R, S*),(*S, S, R*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,06 g, 0,115 mmol, 1 eq) en un pequeño matraz de fondo redondo equipado con una barra de agitación magnética y se disolvió en diclorometano (0,25 ml). A esta reacción se le añadió gota a gota trifluoruro de (dietilamino)azufre (0,152 ml) a temperatura ambiente. Después de 2 horas, la mezcla de reacción se inactivó con la adición de una solución de cloruro de amonio acuoso y se extrajo 3 veces con acetato de etilo. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para dar los compuestos del título con un rendimiento del aislado del 40% (0,024 g, 0,046 mmol).

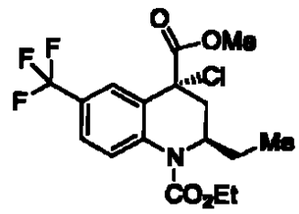
LCMS (ESI+): 524 (MH+).

^{1}H RMN ($CDCl_3$): □ 1,19 (d, 3H), 1,30 (t, 3H), 2,02 (m, 1H), 2,95 (m, 1H), 3,95 (s, 3H9, 3,97 (s, 3H), 4,26 (m, 2H), 4,49 (m, 1H), 6,40 (s, 1H), 6,9 (s, 1H), 7,1 (s,

1H), 7,8 (s, 3H), 7,95 (s, 1H).

Preparación 27





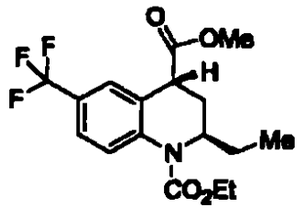
Éster 4-metílico, éster 1-etílico del ácido [(*R.S*) y (*R.R*)]-4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

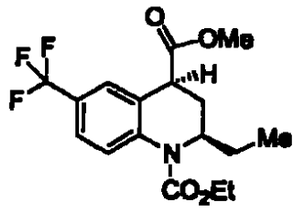
Se introdujo éster etílico del ácido (*R*)-2-etil-4-hidrazono-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico (Preparación 6, 1,22 g, 3,70 mmol) en un matraz de 250 ml de fondo redondo equipado con una barra de agitación magnética. Se añadió éter dietílico (100 ml) seguido de la adición de MnO_2 (22,2 mmol, 6 eq). La reacción se protegió de la luz y se agitó a temperatura ambiente durante 90 minutos. La solución se filtró a través de Celite® y se concentro a un volumen final de 30ml. Se añadió más tolueno (100 ml) y se concentró a 40 ml. A esta solución se le añadió di-*iso*-propiletilamina (3,25 ml, 18,5 mmol) seguido de la adición de una solución de fosgeno al 20% en tolueno (7,5 ml). La mezcla de reacción se agitó durante 45 minutos antes de añadir metanol anhidro (10ml). Después de 2 horas, la reacción se concentró a 20 ml, se extrajo en cloruro de metileno y se lavó con HCl 0,1 N. La capa orgánica se recogió, se secó sobre sulfato de magnesio, se filtró y se concentró a sequedad para obtener el compuesto del título (1,43 g, 3,66 mmol, rendimiento del 98%).

LCMS (ESI+): 394 (MH+).

(*R,S*) y (*R,R*): ^{1}H RMN ($CDCl_3$): □ 0,95 (t, 3H), 1,25 (m, 2H), 1,30 (t, 3H), 2,60 (dd, 1H), 2,79 (dd, 1H), 3,99 (s, 3H), 4,23 (m, 2H), 4,62 (m, H), 761 (d, 1H), 7,70 (d, 1H).

Preparación 28 y 29





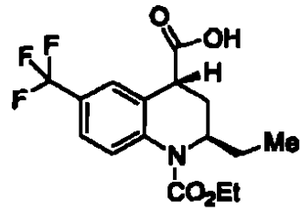
Preparación de éster 4-metílico, éster 1-etílico del ácido [(*R,S*) y (*R,R*)]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico. Se disolvió éster 4-metílico, éster 1-etílico del ácido [(*R,S*) y (*R,R*)]-4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (1,40 gramos, 3,56 mmol) en 30 ml de metanol antes de añadir 0,15 gramos de Pd/C al 10% y la mezcla se hidrogenó a 45 psi en el agitador par durante 2 horas. La mezcla de reacción se filtró a través de Celite y se concentró. La mezcla en bruto se disolvió en diclorometano y la capa orgánica se recogió, se secó sobre sulfato de magnesio y se concentró. El producto se aisló después de cromatografía en columna eluyendo con una solución de 90:10 hexano:acetona para producir 83% (2,98 mmol) del compuesto del título. (*R,S*): ^{1}H RMN ($CDCl_3$): □ 0,84 (t, 3H), 1,30 (t, 3H), 1,40 (m, 2H), 1,95 (m, 1H), 2,47 (m, 1H), 3,61 (m, 1H), 3,80 (s, 3H), 4,3 (m, 2H), 4,42 (m, 1H), 7,40 (s, 1H), 7,60 (d, 1H), 7,70 (d, 1H).

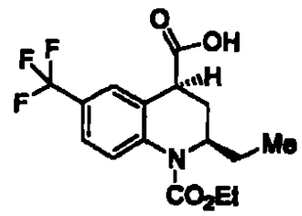
LCMS (ESI+) 360 (MH+)

(*R,R*): ^{1}H RMN ($CDCl_3$): □ 0,86 (t, 3H), 1,18 (t, 3H), 1,38 (m, 2H), 2,1 (m, 1H), 2,56 (m, 1H), 3,69 (s, 3H), 3,90 (t, 1H), 4,30 (m, 2H), 4,58 (m, 1H), 7,46 (s, 1H), 7,50 (d, 1H), 7,70 (d, 1H).

LCMS (ESI+): 360 (MH+)

Preparación 30





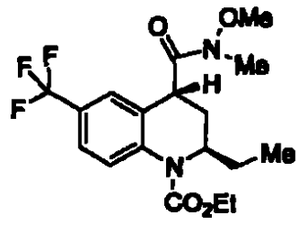
Éster 1-etílico del ácido [(*R,S*) y (*R,R*)]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

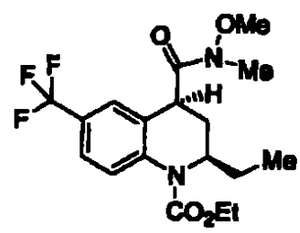
Se disolvió éster 4-metílico, éster 1-etílico del ácido [(*R,S*) y (*R,R*)]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (Preparación 28 y 29, 0,070 g, 0,195 mmol, 1 eq.) en un matraz de fondo redondo con una barra de agitación magnética que contenía dioxano (1,5 ml) y agua (1,5 ml). Se añadió hidróxido sódico (0,016 g, 0,409 mmol, 2,1 eq) y se agitó a temperatura ambiente. Después de 12 horas, la mezcla de reacción se concentró a un volumen mínimo y se repartió entre hidróxido sódico acuoso 1,0N y éter dietílico. La capa acuosa se recogió, se acidificó con ácido clorhídrico concentrado y se extrajo con acetato de etilo. La capa orgánica se recogió, se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar los compuestos del título (0,067 g, 0,194 mmol, rendimiento del 99%).

LCMS (ESI+): 346 (MH+).

[(*R,S*) y (*R,R*)]: ^{1}H RMN ($CDCl_3$): □ 0,84 (t, 3H), 1,23 (t, 3H), 1,39 (m, 2H), 1,94 (m, 1H), 2,59 (m, 1H), 3,84 (t, 1H), 4,19 (m, 2H), 4,62 (m, 2H), 7,49 (m, 2H), 7,63 (d, 1H).

Preparación 31





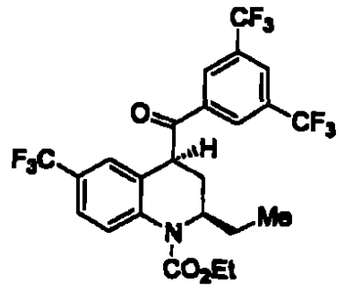
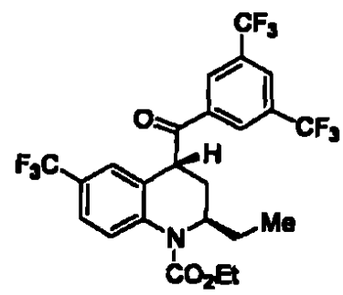
Éster etílico del ácido [(*R,S*) y (*R,R*)]-2-etil-4-(metoxi-metil-carbamoil)-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

Se introdujo éster 1-etílico del ácido [(*R,S*) y (*R,R*)]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (0,066 g, 0,239 mmol) en un matraz de 5 ml de fondo redondo equipado con una barra de agitación. Se añadió cloruro de metileno (3 ml). La mezcla de reacción se enfrió a 0°C. Se añadió di-iso-propiletilamina (0,032 g, 0,248 mmol, 1,3 eq) seguido de la adición de sal *N,O*-dimetilhidroxilamina de HCl (0,239 mmol), 4-dimetilaminopiridina (0,019 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,210 mmol). La reacción se agitó a temperatura ambiente. Después de 12 horas, la reacción se inactivó con agua y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron, se concentraron para proporcionar los compuestos del título (0,065 g, 0,167 mmol, rendimiento del 88%).

LCMS (ESI+): 389 (MH+).

[(*R,S*) y (*R,R*)]: ^{1}H RMN ($CDCl_3$): □ 0,90 (t, 3H), 1,33 (t, 3H), 1,39 (m, 2H), 2,0 (m, 1H), 2,55 (m, 1H), 3,20 (s, 3H), 3,40 (s, 3H), 4,19 (m, 2H), 4,62 (m, 1H), 7,21 (s, 1H), 7,4304 (s, 2H), 7,62 (d, 2H).

Ejemplos 20 y 21

Éster etílico del ácido [(*R,S*) y (*R,R*)]-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

Se disolvió éster etílico del ácido [(*R,S*), (*R,R*)]-2-etil-4-(metoxi-metil-carbamoil)-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (0,564 g, 1,45 mmol, 1 eq.) en tetrahidrofurano (12 ml) en un matraz de fondo redondo equipado con una barra de agitación. La reacción se enfrió a 0ºC. Se añadió gota a gota bromuro de 3,5-bis-(trifluorometil)fenil magnesio (13,6 ml de solución 0,5M) y la mezcla de reacción se agitó a temperatura ambiente. Después de 12 horas, la mezcla de reacción se inactivó con una solución de amoniaco acuoso, posteriormente se saturó con NaCl y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron y se concentraron a sequedad. La cromatografía ultrarrápida eluyendo con 90/10 hexanos/acetato de etilo proporcionó los compuestos del título (0,556 g, 1,02 mmol, rendimiento del 70%).

isómero *trans:*

LCMS (ESI+): 542 (MH+)

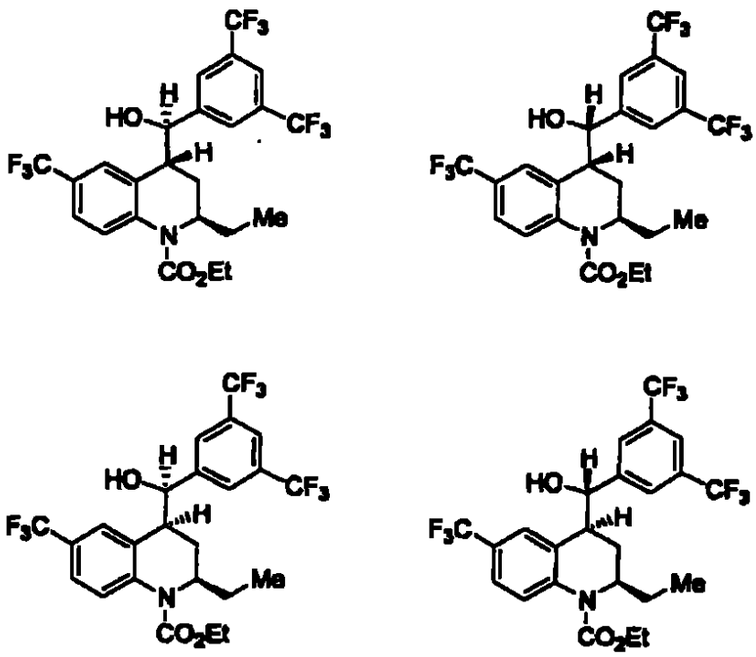
(*R, R*)]: ^{1}H RMN ($CDCl_3$) □ 0,98 (t, 3H), 1,29 (t, 3H), 1,52 (m, 2H), 2,05 (m, 1H), 2,64 (m, 1H), 4,24 (m, 2H), 4,66 (m, 2H), 7,40 (s, 1H), 7,55 (d, 1H), 7,60 (d, 1H), 8,05 (s, 2H), 8,24 (s, 1H).

isómero *cis:*

LCMS (ESI+): 542 (MH+)

(*R, S*): ^{1}H RMN ($CDCl_3$) □ 0,91 (t, 3H), 1,39 (t, 3H), 1,43 (m, 2H), 1,78 (m, 1H), 1,99 (m, 1H), 2,60 (m, 1H), 4,34 (m, 2H), 4,56 (m, 2H), 7,05 (s, 1H), 7,55 (d, 1H), 7,65 (d, 1H), 8,20 (s,1H), 8,44 (s, 2H).

Ejemplos 22, 23, 24 y 25



Éster etílico del ácido [(*R, R, R*)], [(*R, R, S*)], [(*R, S, S*)] y [(*R, S, R*)]-4-(3,5-bis-trifluorometil-fenil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se introdujo éster etílico del ácido [(*R,S*) y (*R,R*)]-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (0,182 g, 0,34 mmol, 1 eq.) en un matraz de fondo redondo equipado con una barra de agitación magnética. Se añadió metanol (6,8 ml) seguido de la adición de (0,077 g, 2,05 mmol, 6 eq) de borohidruro sódico a temperatura ambiente. Después de 1 hora, la mezcla de

reacción se inactivó con una solución de salmuera, se extrajo tres veces con acetato de etilo y se secó sobre sulfato sódico. El material se purificó por cromatografía ultrarrápida eluyendo con 90/10 hexanos/acetato de etilo para proporcionar los compuestos del título en tres fracciones:

(*R, S, R*):

LCMS (ESI+): 544 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,81 (t, 3H), 1,27 (t, 3H), 2,04 (m, 1H), 4,22 (m, 3H), 7,86 (s, 1H), 7,90 (s, 1H).

(*R, S, S*):

LCMS (ESI+): 544 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,73 (t, 3H), 1,09 (m, 1H), 1,27 (t, 3H), 1,43 (m, 2H), 1,67 (m, 1H), 2,44 (d, 1H), 2,87 (m, 1H), 4,24 (m, 3H), 5,17 (dd, 1H), 7,26 (s, 1H), 7,50 (m, 2H), 7,90 (s, 2H), 7,92 (s, 1H).

(*R, R, R*) y (*R, R, S*): Esta mezcla se separó en una columna de 10 x 50 cm Chiralpak AD eluyendo en heptano/IPA 98/2 con un caudal de 275 ml/min.

(*R, R, R*): ^{1}H RMN ($CDCl_3$): □ 0,77 (t, 3H), 1,31 (t, 3H), 1,41 (m, 2H), 2,21 (d, 1H), 3,19 (m, 1H), 4,23 (m, 2H), 4,37 (m, 1H), 4,83 (d, 1H), 765 (s, 2H), 7,79 (s, 1H).

LCMS (ESI+): 544 (MH+)

(*R, R, S*): ^{1}H RMN ($CDCl_3$): □ 0,81 (t, 3H), 1,33 (t, 3H), 1,6 (m, 2H), 2,22 (d, 1H), 3,05 (m, 1H), 4,30 (m, 2H), 4,6 2(m, 1H), 5,19 (d, 1H), 7,01 (s, 1H), 7,40 (s, 2H), 7,85 (s, 1H).

LCMS (ESI+): 544 (MH+)

Preparaciones 32 y 33

Éster etílico del ácido [(*R, R*) y (*S, S*)] y [(*S, R*) y (*R, S*)]-4-aminometil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

Se suspendió borohidruro sódico (0,828 g, 21,9 mmol) en tetrahidrofurano (13,5 ml) en un matraz seco de 50 ml con fondo redondo equipado con una barra de agitación. En otro matraz se disolvió ácido trifluoroacético (1,68 ml, 21,8 mmol) en tetrahidrofurano (5 ml). El matraz de reacción de 50 ml se enfrió a 0°C y se añadió lentamente la solución de ácido trifluoroacético. La reacción se dejó en agitación a temperatura ambiente. Después de 30 minutos se añadió gota a gota a la reacción éster etílico del ácido [(*R*, *R*), (*S*, *S*)] y [(*S*, *R*) , (*R*, *S*)]-4-ciano-6,7-dimetoxi-2metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (1,33 g, 4,37 mmol) en tetrahidrofurano (5 ml). Después de 12 horas, la reacción se enfrió a 0°C y se inactivó cuidadosamente con agua. La capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas se combinaron, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El producto en bruto se purificó por cromatografía ultrarrápida eluyendo con 97/2/1 de cloruro de metileno/metanol/trietilamina para producir los compuestos del título (0,982 g, 3,18 mmol, rendimiento del 73%).

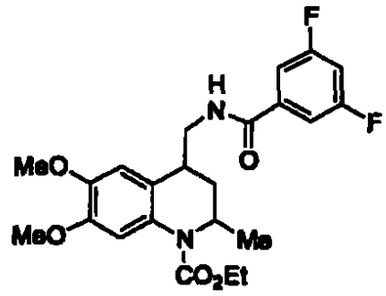
LCMS (ESI+): 309 (MH+)

[(*R*, *S*), (*S*, *R*)]: ^{1}H RMN ($CDCl_3$) □ 1,18 (d, 3H), 1,27 (t 3H), 2,47 (m, 2H), 2,92 (m, 4H), 3,29 (m, 1H), 3,84 (s, 3H), 3,86 (s, 3H), 4,19 (m, 2H), 4,47 (m, 1H), 6,69 (s, 1H), 7,02 (s, 1H).

LCMS (ESI+): 309 (MH+)

[(*R*, *R*), (*S*, *S*)]: ^{1}H RMN ($CDCl_3$) □ 1,15 (d, 3H), 1,31 (t, 3H), 1,76 (m, 1H), 2,18 (m, 2H), 2,94 (m, 3H), 3,85 (s, 3H), 3,86 (s, 3H), 4,22 (m, 2H), 4,61 (m, 1H), 6,69 (s, 1H), 7,12 (s, 1H).

Ejemplo 26



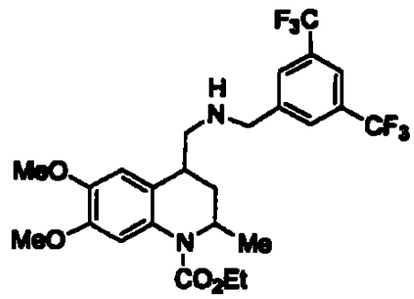
Éster etílico del ácido [(*R, S*) y (*R, R*)] y [(*S ,S*) y (*S, R*)]-4-[(3,5-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico

A una solución de éster etílico del ácido [(*R, S*) y (*S, S*)] y [(*S ,R*) y (*R, S*)]-4-aminometil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1,4-dicarboxílico (0,012 g, 0,039 mmol) en cloruro de metileno (1,0 ml) se le añadió ácido 3,5-difluorobenzoico (0,0065 g, 0,041 mmol, 1,0 eq) seguido de clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,012 g, 0,065 mmol, 1,6 eq) e hidrato de 1-hidroxibenzotriazol (0,005 g, 0,039 mmol, 1 eq). La reacción se agitó a temperatura ambiente durante 12 horas. La mezcla se concentró, se disolvió en dimetilsulfóxido y se purificó por HPLC para proporcionar el compuesto del título (0,008 g, 0,019 mmol).

LCMS (ESI+): 449 (MH+)

[(*R, S*), (*R, R*)] y [(*S, S*), (*S, R*)]: ^{1}H RMN ($CDCl_3$) □ 1,15 (d, 3H), 1,30 (t, 3H), 1,79 (m, 1H), 2,16 (m, 1H), 3,16 (m, 1H), 3,63 (m, 2H), 3,82 (s, 3H), 3,87 (s, H), 4,22 (m, 2H), 4,63 (m, 1H), 6,13 (m, 1H), 6,63 (s, 1H), 6,92 (m, 1H), 7,13 (s, 1H), 7,19 (m, 2H).

Ejemplos 27 y 28



Éster etílico del ácido [(*R*, *S*) y (*S*, *R*)] y [(*R* , *R*) y (*S*, *S*)]-4-[(3,5-bis-trifluorometil-bencilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se disolvió éster etílico del ácido [(*R*, *S*) y (*S*, *R*)] y [(*S* ,*S*) y (*R*, *R*)]-4-aminometil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,131 g, 0,428 mmol) en dicloroetano (2,0 ml) en un matraz de 10 ml con fondo redondo equipado con una barra de agitación. A esta solución, se le añadió 3,5-bis(trifluorometil)benzaldehído (0,071 ml, 0,431 mmol) seguido de triacetoxiborohidruro sódico (0,272 g, 1,28 mmol). Después de agitar a temperatura ambiente durante 12 horas, la mezcla de reacción se inactivó con una solución acuosa de hidróxido sódico 1 N y se extrajo 3 veces con acetato de etilo. Las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron y se concentraron. La purificación por cromatografía ultrarrápida eluyendo con 80/20 hexanos/acetato de etilo proporcionó los compuestos del título (0,063 g, 0,12 mmol, rendimiento del 28%).

LCMS (ESI+): 535 (MH+)

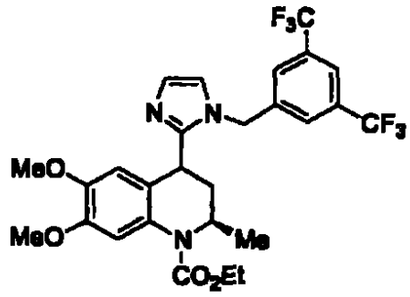
[(*R*, *S*), (*S*, *R*)]: ^{1}H RMN ($CDCl_3$): □ 1,09 (m, 1H), 1,17 (d, 3H), 1,28 (t, 3H), 2,47 (m, 1H), 2,61 (m, 1H), 2,83 (m, 1H), 3,16 (m, 1H), 3,83 (s, 3H), 3,84 (s, 3H), 4,02 (s, 2H), 4,20 (m, 2H), 4,47 (m, 1H), 6,81 (s, 1H), 7,01 (s, 1H), 7,82 (s, 1H), 7,87 (s, 2H).

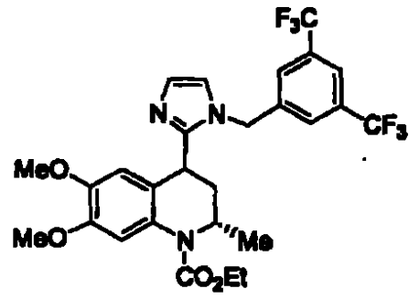
LCMS (ESI+): 535 (MH+)

[(*R*, *R*), (*S*, *S*)]: ^{1}H RMN ($CDCl_3$): □ 1,14 (d, 3H), 1,28 (t, 3H), 1,74 (m, 1H),

2,21 (m, 1H), 2,79 (m, 2H), 2,93 (m, 1H), 3,83 (s, 3H), 3,84 (s, 3H), 3,88 (s, 2H), 4,20 (m, 2H), 4,56 (s, 1H), 6,69 (s, 1H), 7,11 (s, 1H), 7,75 (s, 1H), 7,79 (s, 2H).

Ejemplos 29 y 30





Éster etílico del ácido [(*R*, *S*) y (*S*, *R*)] y [(*R* , *R*) y (*S*, *S*)]-4-[(3,5-bis-trifluorometil-bencil)-metoxicarbonil-amino]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se disolvió éster etílico del ácido [(*R*, *S*) y (*S*, *R*)] y [(*S* , *S*) y (*R*, *R*)]-4-[(3,5-bis-trifluorometil-bencilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,020 g, 0,037 mmol) en tetrahidrofurano (2,0 ml) en un matraz de 10 ml de fondo redondo equipado con una barra de agitación. A esta solución se le añadió carbonato de potasio (0,134 g, 0,972 mmol) seguido de la adición de cloroformiato de metilo (0,030 ml, 0,388 mmol). La mezcla de reacción se agitó a temperatura ambiente. Después de 12 horas, la mezcla de reacción se inactivó con hidróxido sódico acuoso 1,0N y se extrajo tres veces con acetato de etilo. las capas orgánicas se recogieron, se secaron sobre sulfato sódico, se filtraron y se concentraron. La purificación por cromatografía ultrarrápida eluyendo con 65/35 hexanos/acetato de etilo proporcionó los compuestos del título (0,005 g, 0,008 mmol, rendimiento del 30%).

LCMS (ESI+): 593 (MH+)

[(*R*, *S*), (*S*, *R*)]: ^{1}H RMN ($CDCl_3$): □ 1,17 (d, 3H), 1,29 (t, 3H), 2,30 (m, 1H),

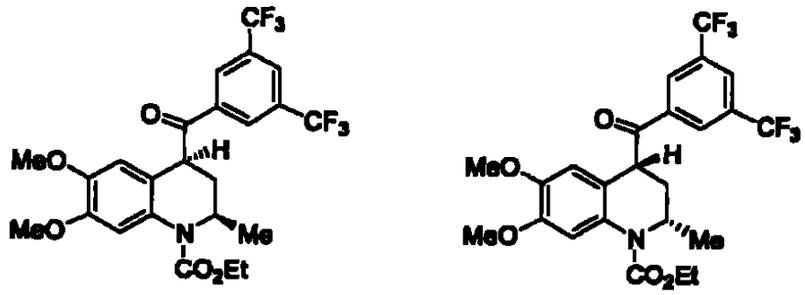
2,75 (m, 1H), 3,60 (m, 1H), 3,78 (s, 3H), 3,83 (s, 3H), 3,85 (s, 3H), 4,22 (m, 2H), 4,39 (m, 1H), 7,03 (s, 1H).

LCMS (ESI+): 593 (MH+)

[(*R*, *R*), (*S*, *S*)]: ^{1}H RMN ($CDCl_3$): □ 1,15 (d, 3H), 1,24 (m, 3H), 1,63 (m, 1H), 2,15 (m, 1H), 3,78 (s, 3H), 3,83 (s, 3H), 3,86 (s, 3H), 4,17 (m, 2H), 4,53 (m, 1H), 7,06 (s, 1H).

Los siguientes ejemplos se prepararon con materiales de partida análogos usando procedimientos análogos a aquellos descritos en los ejemplos anteriores.

Ejemplo 31

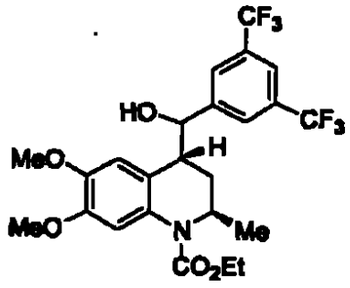


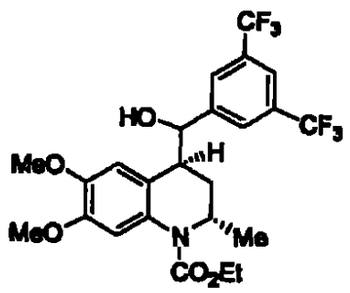
Éster etílico del ácido [(*R*, *S*) y (*S*, *R*)] -4-[(3,5-bis-trifluorometil-benzoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 1,2 (d, 3H), 1,35 (t, 3H), 1,95 (m, 1H), 2,55 (m, 1H), 3,60 (s, 3H), 3,97 (s, 3H), 4,20 (m, 1H), 4,22 (m, 1H), 4,40 (m, 1H), 4,62 (m, 1H), 6,2 (s, 1H), 7,1 (s, 1H), 8,19 (s, 1H), 8,45 (s, 2H).

LCMS (ESI+): 522 (MH+).

Ejemplo 32



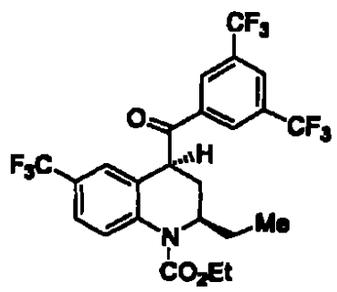


Éster etílico del ácido [(*R, S, S*)], [(*S, R, R*)], [(*R, S, R*)] y [(*S, R, S*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 1,13 (d, 3H), 1,34 (t, 3H), (m, 1H), 2,97 (m, 1H), 3,87 (s, 3H), 3,88 (s, 3H), 4,26 (m, 2H), 4,40 (m, 1H), 5,05 (d, 1H), 6,89 (s, 1H), 6,99 (s, 1H), 7,84 (s, 3H).

LCMS (ESI+): 522 (MH+).

Ejemplo 33

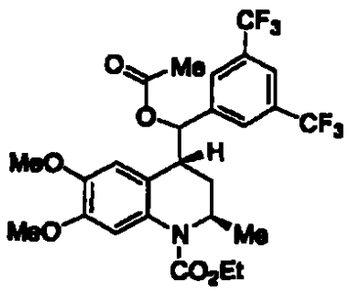
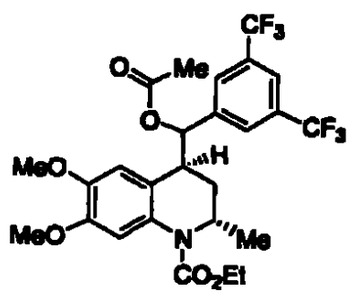


Éster etílico del ácido (*R, S*)-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

(*R, S*)]- cis: ^{1}H RMN ($CDCl_3$): □ 0,91 (t, 3H), 1,39 8t, 3H), 1,43 (m, 2H), 1,78 (m, 1H), 1,99 (m, 1H), 2,60 (m, 1H), 4,34 (m, 2H), 4,56 (m, 2H), 7,05 (s, 1H), 7,55 (d, 1H), 7,65 (d, 1H), 8,20 (s, 1H), 8,44 (s, 2H).

LCMS (ESI+): 542 (MH+).

Ejemplo 34

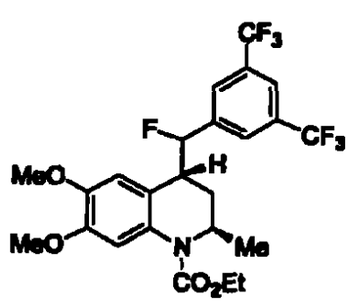
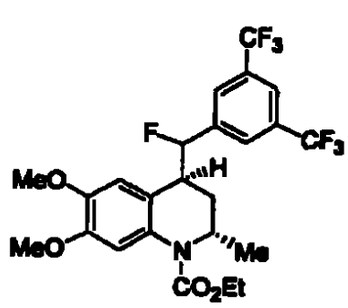



Éster etílico del ácido [(*R*, *R*, *S*)], [(*S*, *S*, *R*)], [(*R*, *R*, *R*)] y [(*S*, *S*, *S*)]-4-[Acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 1,10 (d, 3H), 1,29 (t, 3H), 1,62 (m, 1H), 1,87 (m, 1H), 2,00 (s, 3H), 3,22 (m, 1H), 3,84 (s, 3H), 3,86 (s, 3H), 4,21 (m, 2H), 4,47 (m, 1H), 5,89 (d, 1H), 6,62 (s, 1H), 7,03 (s, 1H), 7,66 (s, 2H), 7,80 (s, 1H).

LCMS (ESI+): 564 (MH+).

Ejemplo 35

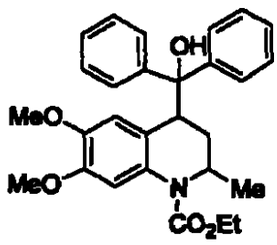
Éster etílico del ácido [(*R*, *R*, *R*)], [(*S*, *S*, *S*)], [(*R*, *R*, *S*)] y [(*S*, *S*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 1,19 (d, 3H), 1,30 (t, 3H), 2,02 (m, 1H), 2,95 (m,1H), 3,95 (s, 3H), 3,97 (s, 3H), 4,26 (m, 2H), 4,49 (m, 1H), 6,40 (s, 1H), 6,9 (s, 1H), 7,1 (s, 1H),

7,8 (s, 3H), 7,95 (s, 1H).

LCMS (ESI+): 524 (MH+).

Ejemplo 36

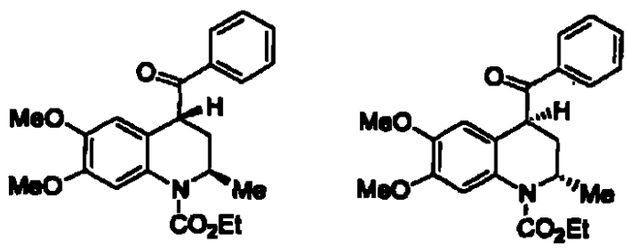


Éster etílico del ácido [(*R*, *R*), (*S*, *S*), (*R*, *S*), (*S*, *R*)]-4-(hidroxi-difenil-metil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 1,0 (d, 3H), 1,32 (t, 3H), 2,2 (m,1H), 3,90 (s, 3H), 3,95 (s, 3H), 4,26 (m,2 H), 4,6 (m, 1H), 6,60 (s, 1H), 6,9 (s, 1H), 7,0 (s, 1H), 7,2-7,4 (m, 10H).

LCMS (ESI+): 444 (MH+) (menos grupo 17OH).

Ejemplo 37

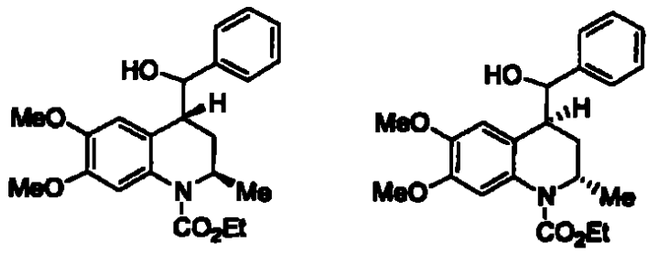


Éster etílico del ácido [(*R*, *R*), (*S*, *S*)]-4-benzoil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 1,19 (d, 3H), 1,25 (t, 3H), 2,4 (m, 1H), 3,75 (s, 3H), 3,85 (s, 3H), 4,30 (m, 2H), 4,6 (m, 1H), 4,9 (m, 1H), 6,50 (s, 1H), 7,2 (s, 1H), 7,4 (m, 2H), 7,5 (t, 1H), 7,9 (d, 2H).

LCMS (ESI+): 384 (MH+)

Ejemplo 38



Éster etílico del ácido [(*R*, *S*, *S*), (*R*, *S*, *R*), (*S*, *R*, *R*), (*S*, *R*, *S*)]-4-(hidroxi-fenil-metil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 386 (MH+)

Los ejemplos 39-169 de la Tabla A se prepararon en forma de mezclas racémicas usando procedimientos análogos a los descritos anteriormente con los materiales de partida apropiados y tienen la siguiente estructura:

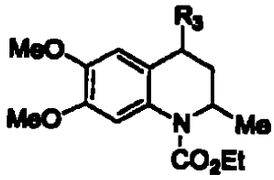
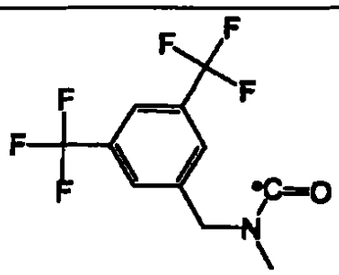
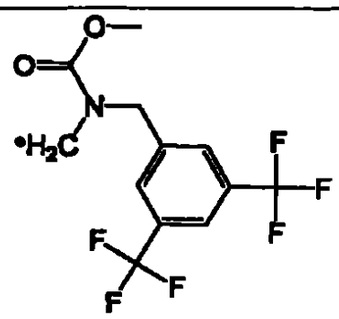
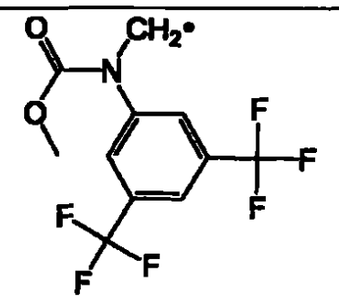
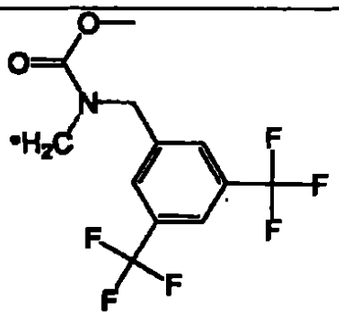
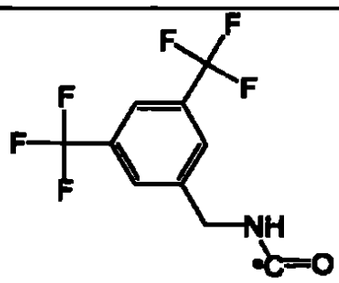
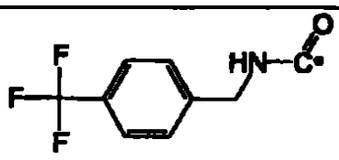
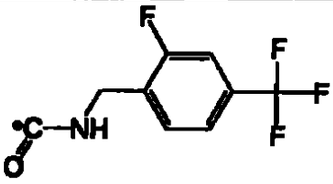
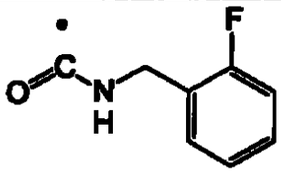
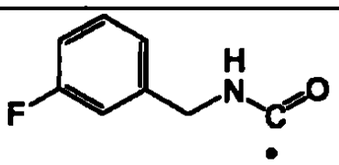
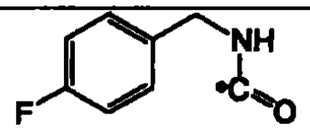
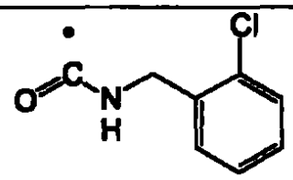
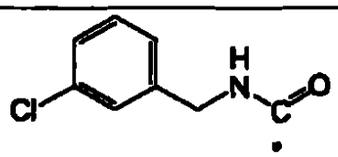
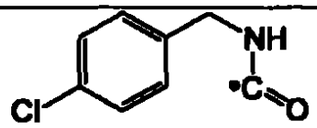
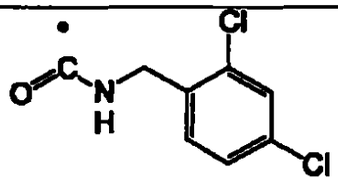
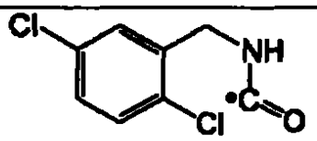
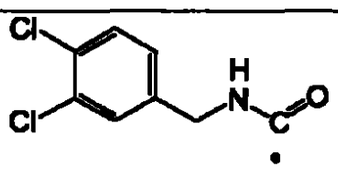
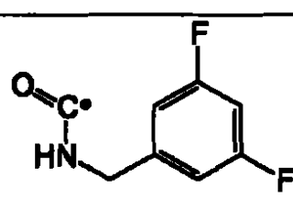


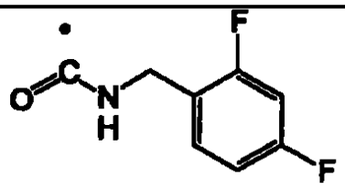
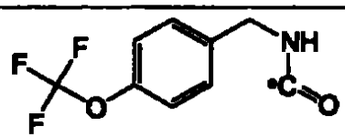
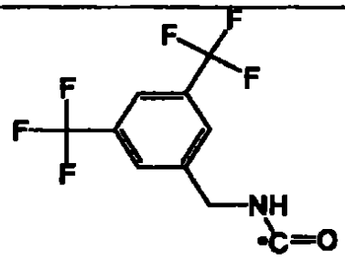
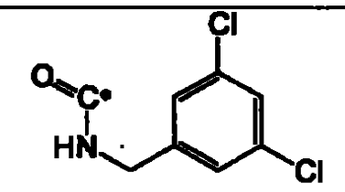
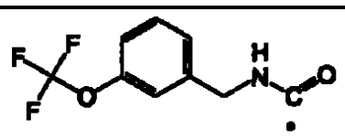
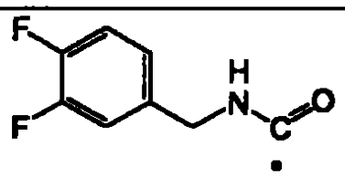
Tabla A

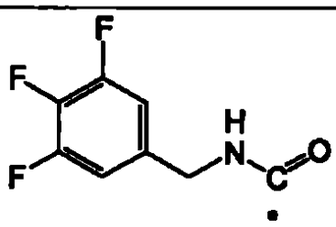
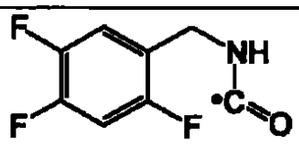
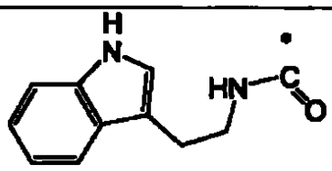
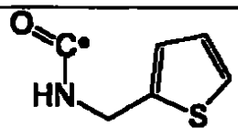
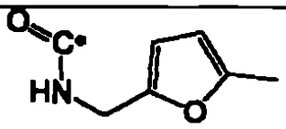
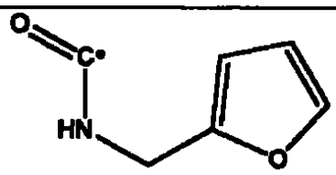
Ej.	R^3 (· denota enlace con la estructura)	Compuesto	LCMS ESI+ (MH+)

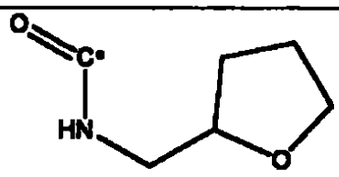
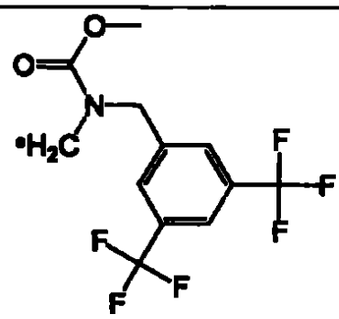
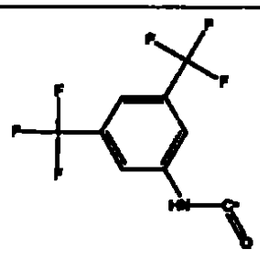
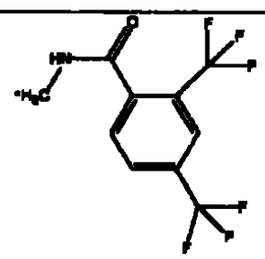
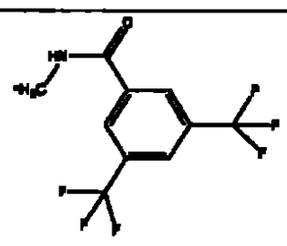
39		Éster etílico del ácido 4-[(3,5-bis-trifluorometil-bencil)-metil-carbamoil]-6,7-dimetoxi-2-metil-5933,4-dihidro-2*H*-quinolin-1-carboxílico	563
40		Éster etílico del ácido 4-{[(3,5-bis-trifluorometil-bencil)-metoxicarbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	579
41		Éster etílico del ácido 4-{[(3,5-bis-trifluorometil-fenil)-metoxi-carbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	
42		Éster etílico del ácido 4-{[(3,5-bis-trifluorometil-bencil)-metoxi-carbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	593

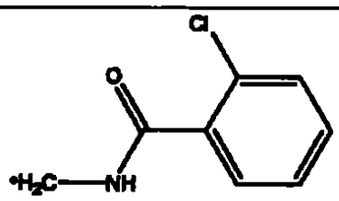
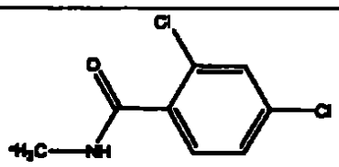
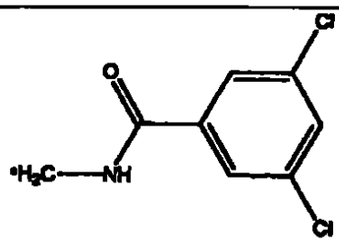
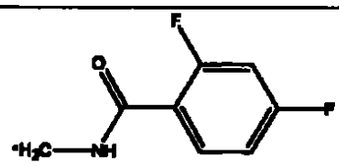
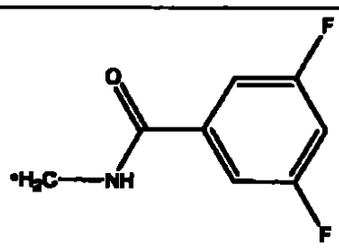
43		Éster etílico del ácido 4-(3,5-bis-trifluorometil-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	549
44		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-(4-trifluorometil-bencilcarbamoil)-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
45		Éster etílico del ácido 4-(2-fluoro-4-trifluorometil-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
46		Éster etílico del ácido 4-(2-fluoro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	431
47		Éster etílico del ácido 4-(3-fluoro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	431
48		Éster etílico del ácido 4-(4-fluoro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	431

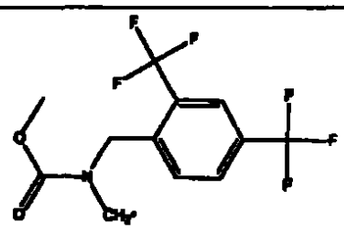
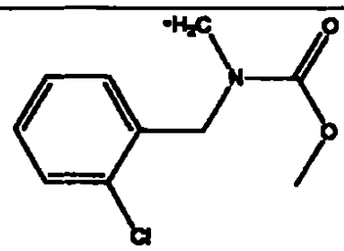
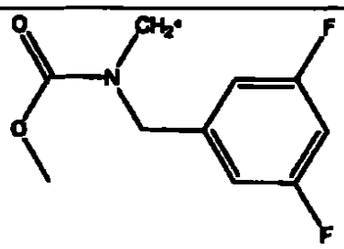
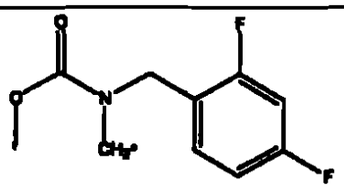
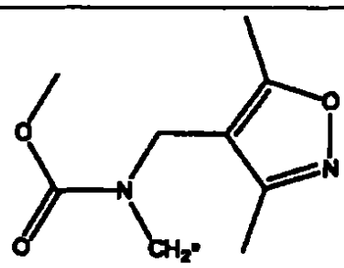
49		Éster etílico del ácido 4-(2-cloro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	447
50		Éster etílico del ácido 4-(3-cloro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	447
51		Éster etílico del ácido 4-(4-cloro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	447
52		Éster etílico del ácido 4-(2,4-dicloro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
53		Éster etílico del ácido 4-(2,5-dicloro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
54		Éster etílico del ácido 4-(3,4-dicloro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
55		Éster etílico del ácido 4-(3,5-difluoro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449

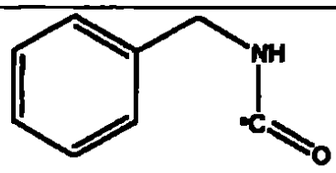
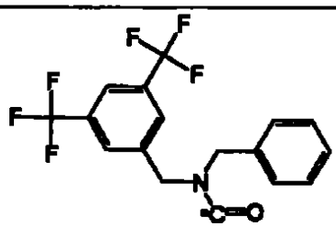
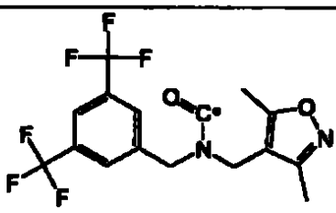
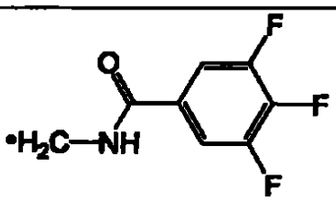
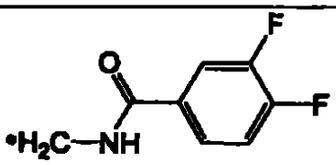
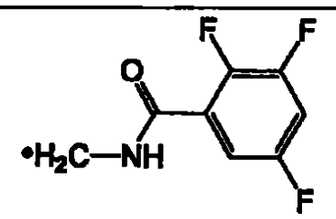
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57		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-(4-trifluorometoxi-bencilcarbamoil)-3,4-dihidro-2*H*-quinolin-1-carboxílico	497
58		Éster etílico del ácido 4-(3,5-bis-trifluorometil- bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	549
59		Éster etílico del ácido 4-(3,5-dicloro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
60		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-(3-trifluorometoxi-bencilcarbamoil)-3,4-dihidro-2*H*-quinolin-1-carboxílico	497
61		Éster etílico del ácido 4-(3,4-difluoro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	467

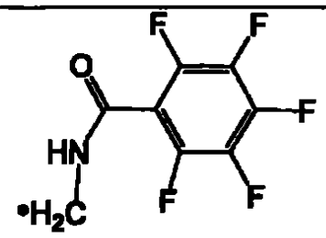
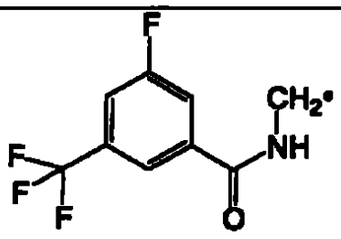
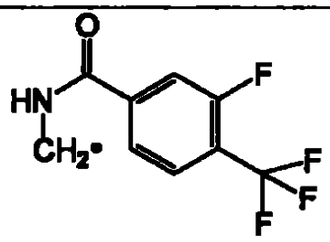
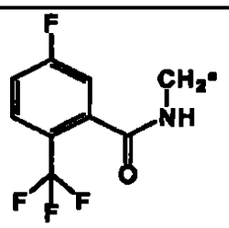
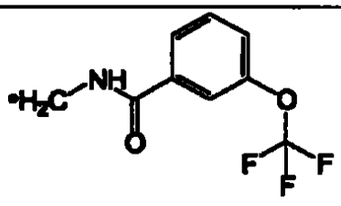
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63		Éster etílico del ácido 4-(2,4,5-trifluoro-bencilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	467
64		Éster etílico del ácido 4-[2-(1H-indol-3-il)-etilcarbamoil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	466
65		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(tiofen-2-ilmetil)-carbamoil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	419
66		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(5-metil-furan-2-ilmetil)-carbamoil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	417
67		Éster etílico del ácido 4-[(Furan-2-ilmetil)-carbamil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	403

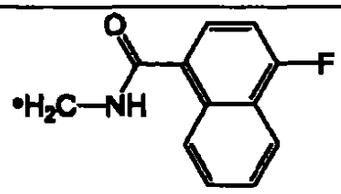
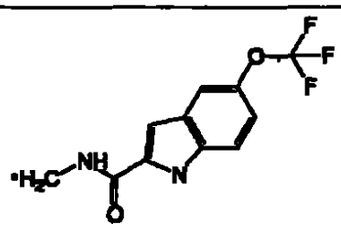
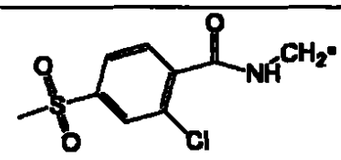
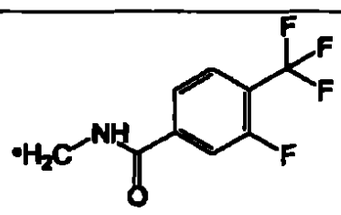
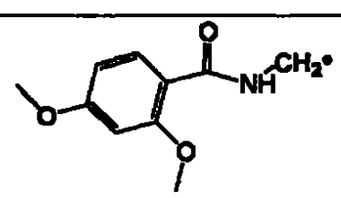
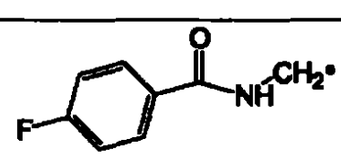
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69		Éster etílico del ácido 4-{[(3,5-bis-trifluorometil-bencil)-metoxi-carbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	593
70		Éster etílico del ácido 4-(3,5-bis-trifluorometil-fenilcarbamoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	535
71		Éster etílico del ácido 4-[(2,4-bis-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	549
72		Éster etílico del ácido 4-[(3,5-bis-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	549

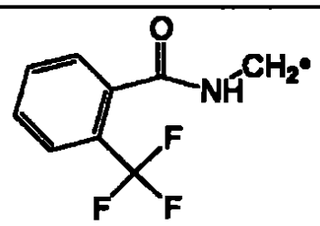
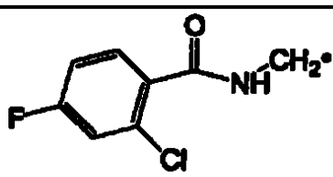
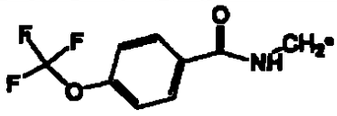
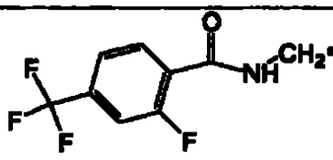
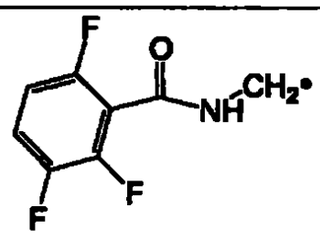
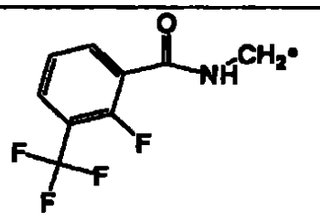
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74		Éster etílico del ácido 4-[(2,4-dicloro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
75		Éster etílico del ácido 4-[(3,5-dicloro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
76		Éster etílico del ácido 4-[(2,4-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449
77		Éster etílico del ácido 4-[(3,5-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449

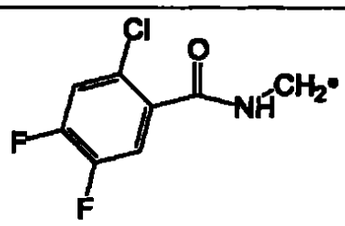
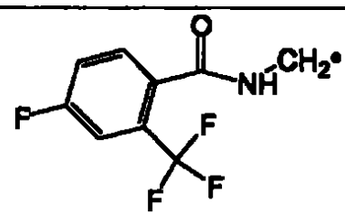
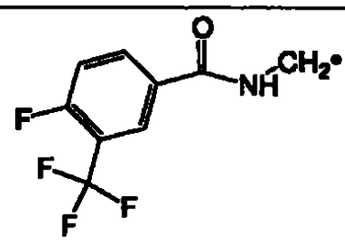
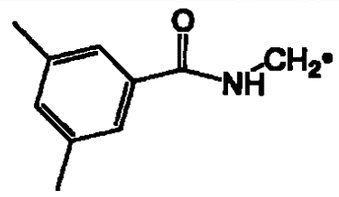
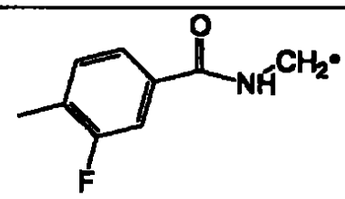
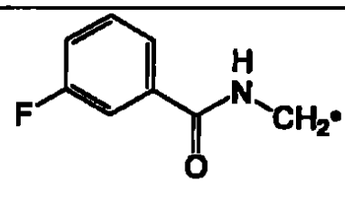
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79		Éster etílico del ácido 4-{[(2-cloro-bencil)-metoxicarbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	491
80		Éster etílico del ácido 4-{[(3,5-difluoro-bencil)-metoxicarbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	493
81		Éster etílico del ácido 4-{[(2,4-difluoro-bencil)-metoxicarbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	493
82		Éster etílico del ácido 4-{[(3,5-dimetil-isoxazol-4-ilmetil)-metoxicarbonil-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	476

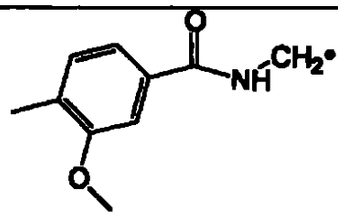
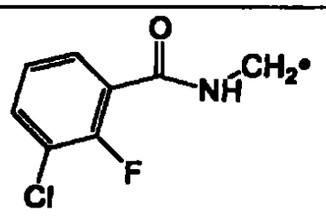
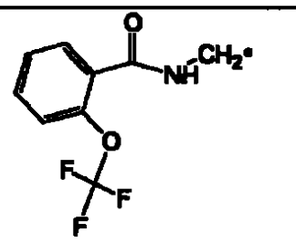
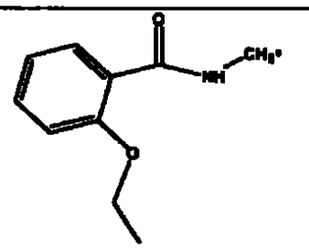
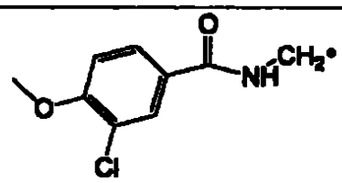
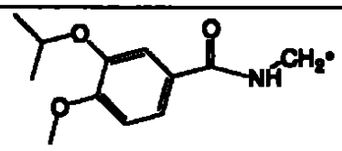
83		Éster etílico del ácido 4-bencilcarbamoil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	413
84		Éster etílico del ácido 4-[bencil-(3,5-bis-trifluorometil-bencil)-carbamoil-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	639
85		Éster etílico del ácido 4-[(3,5-bis-trifluorometil-bencil)-(3,5-dimetil-isoxazol-4-ilmetil)-carbamoil] -6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	658
86		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(3,4,5-trifluoro-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	467
87		Éster etílico del ácido 4-[(3,4-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449
88		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(2,3,5-trifluoro-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	467

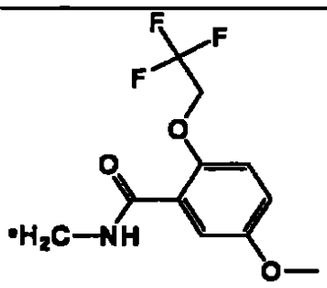
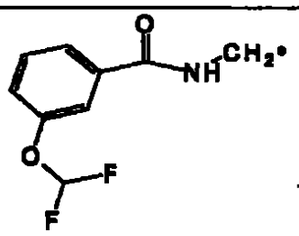
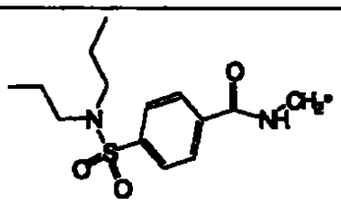
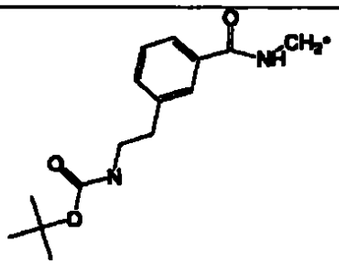
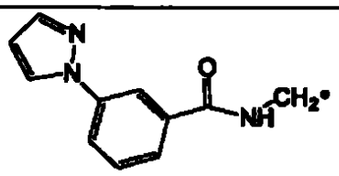
89		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(2,3,4,5,6-pentafluorobencenoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	503
90		Éster etílico del ácido 4-[(3-fluoro-5-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
91		Éster etílico del ácido 4-[(3-fluoro-4-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
92		Éster etílico del ácido 4-[(5-fluoro-2-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
93		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(3-trifluorometoxi-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	497

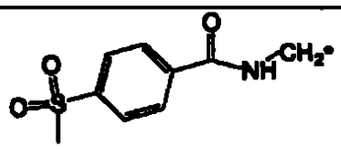
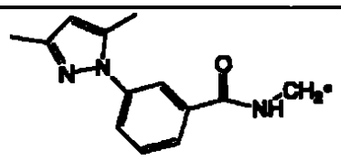
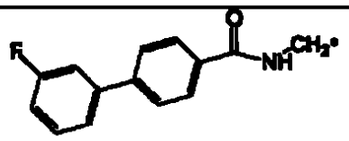
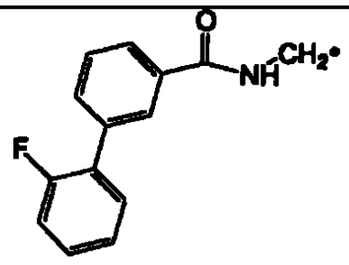
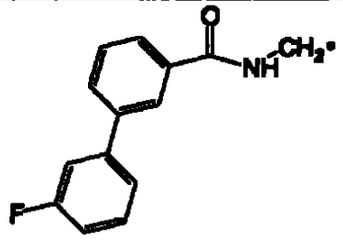
94		Éster etílico del ácido 4-{[(4-fluoro-naftalen-1-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
95		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-{[(5-trifluorometoxi-1H-indol-2-carbonil)-amino]-metil}-3,4-dihidro-2*H*-quinolin-1-carboxílico	536
96		Éster etílico del ácido 4-{[(2-cloro-4-metanosulfonil-benzoilamino)-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	525
97		Éster etílico del ácido 4-[(3-fluoro-4-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
98		Éster etílico del ácido 4-[(2,4-dimetoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	473
99		Éster etílico del ácido 4-[(4-fluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	431

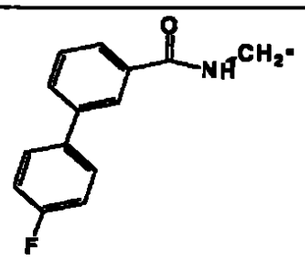
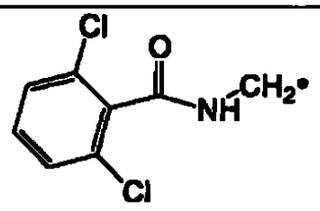
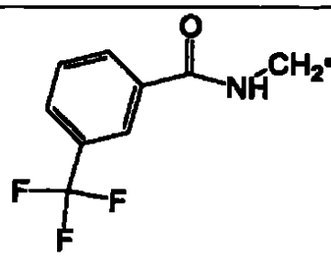
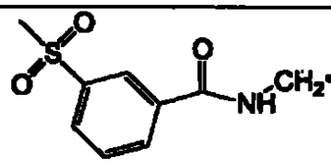
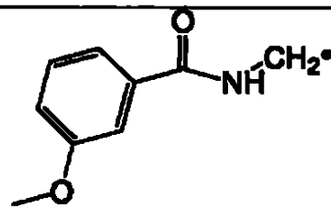
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101		Éster etílico del ácido 4-[(2-cloro-4-fluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	465
102		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(4-trifluorometoxi-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	497
103		Éster etílico del ácido 4-[(2-fluoro-4-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
104		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(2,3,6-trifluoro-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	467
105		Éster etílico del ácido 4-[(2-fluoro-3-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499

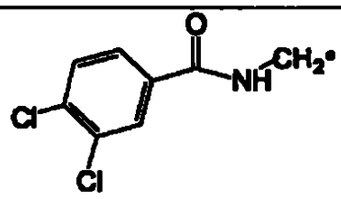
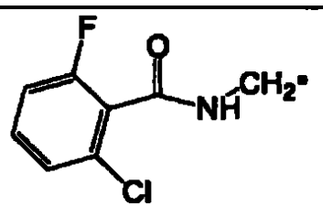
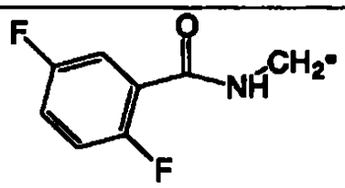
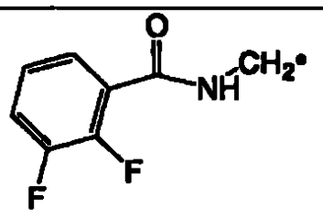
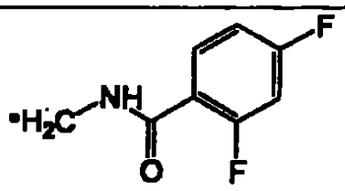
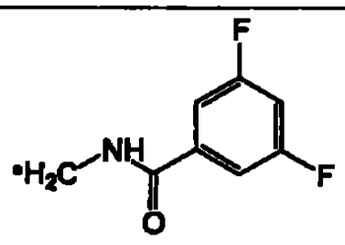
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107		Éster etílico del ácido 4-[(4-fluoro-2-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
108		Éster etílico del ácido 4-[(4-fluoro-3-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
109		Éster etílico del ácido 4-[(3,5-dimetil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	441
110		Éster etílico del ácido 4-[(3-fluoro-4-metil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	445
111		Éster etílico del ácido 4-[(3-fluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	431

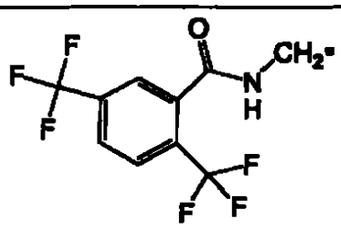
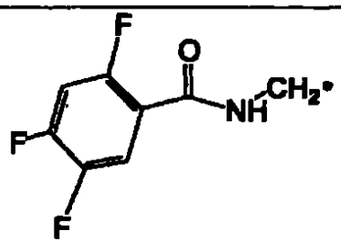
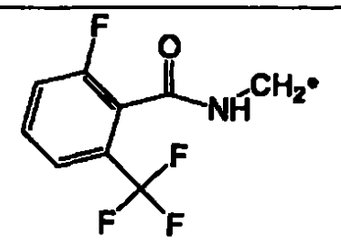
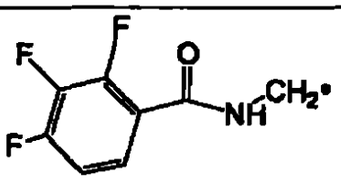
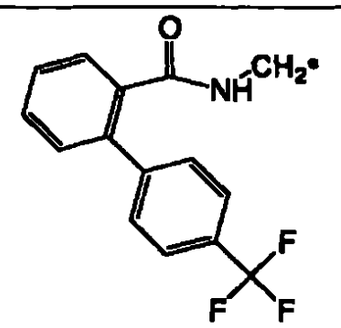
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113		Éster etílico del ácido 4-[(3-cloro-2-fluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	465
114		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(2-trifluorometoxi-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	497
115		Éster etílico del ácido 4-[(3-etoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	457
116		Éster etílico del ácido 4-[(3-cloro-4-metoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	477
117		Éster etílico del ácido 4-[(3-isopropoxi-4-metoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	501

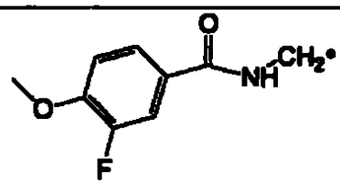
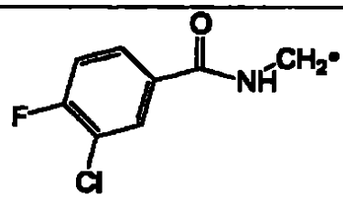
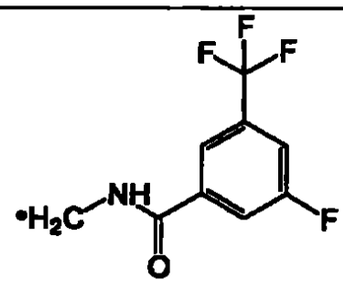
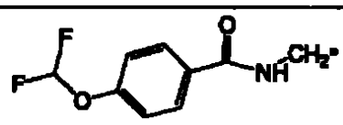
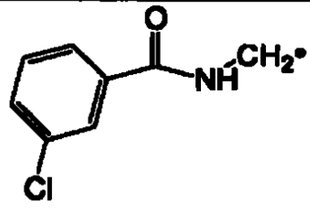
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119		Éster etílico del ácido 4-[(3-difluorometoxi- benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	479
120		Éster etílico del ácido 4-[(4-dipropilsulfamoil--benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	576
121		Éster etílico del ácido 4-{[3-(2-terc-butoxicarbonilamino-etil)-benzoilamino)-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	556
122		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(3-pirazol-1-il-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	479

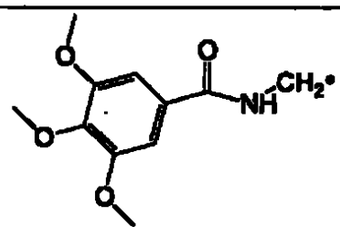
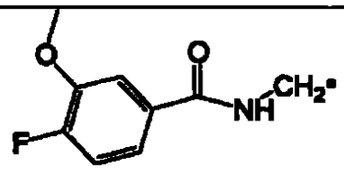
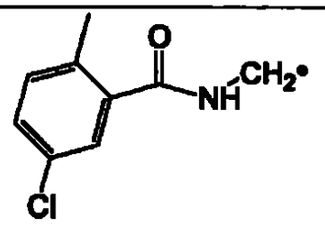
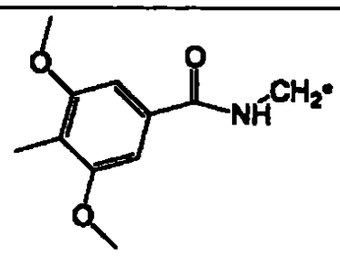
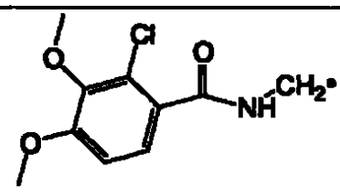
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124		Éster etílico del ácido 4-{[3-(3,5-dimetil-pirazol-1-il)-benzoilamino)-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	507
125		Éster etílico del ácido 4-{[3'-fluoro-bifenil-4-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	507
126		Éster etílico del ácido 4-{[2'-fluoro-bifenil-3-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	507
127		Éster etílico del ácido 4-{[3'-fluoro-bifenil-3-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	507

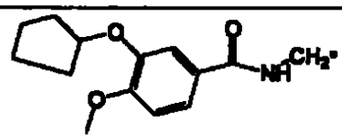
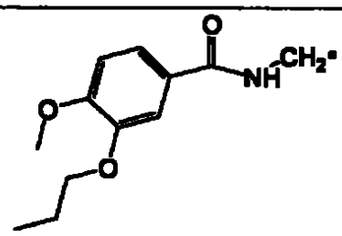
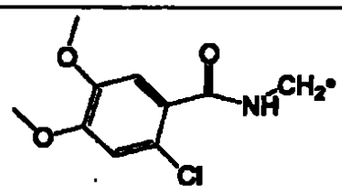
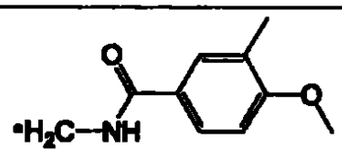
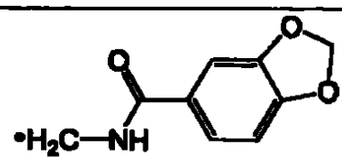
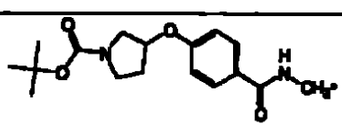
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129		Éster etílico del ácido 4-[(2,6-dicloro-benzoilamino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
130		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(3-trifluorometil-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
131		Éster etílico del ácido 4-[(3-metanosulfonil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	491
132		Éster etílico del ácido 6,7-dimetoxi-4-[(3-metoxi- benzoilamino)-metil]-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	443

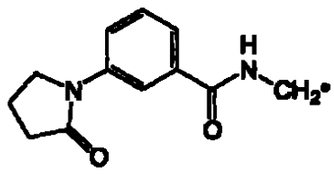
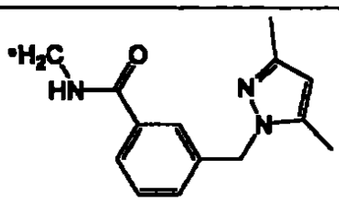
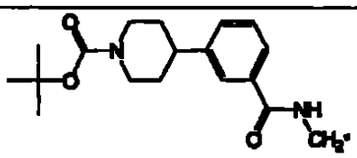
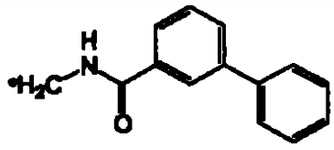
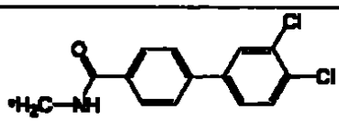
133		Éster etílico del ácido 4-[(3,4-dicloro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	481
134		Éster etílico del ácido 4-[(2-cloro-6-fluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	465
135		Éster etílico del ácido 4-[(2,5-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449
136		Éster etílico del ácido 4-[(2,3-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449
137		Éster etílico del ácido 4-[(2,4-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449
138		Éster etílico del ácido 4-[(3,5-difluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449

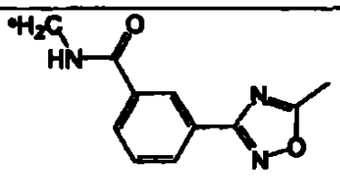
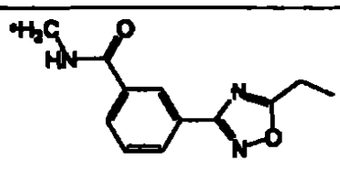
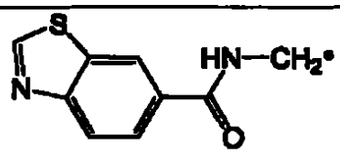
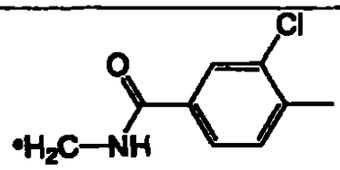
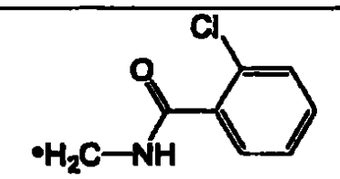
139		Éster etílico del ácido 4-[(2,5-bis-trifluorometil- benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	449
140		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(2,4,5-trifluoro-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	467
141		Éster etílico del ácido 4-[(2-fluoro-6-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
142		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(2,3,4-trifluoro-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	467
143		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-{[(4'-trifluorometil-bifenil-2-carbonil)-amino]-metil}-3,4-dihidro-2*H*-quinolin-1-carboxílico	557

144		Éster etílico del ácido 4-[(3-fluoro-4-metoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	461
145		Éster etílico del ácido 4-[(3-cloro-4-fluoro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	465
146		Éster etílico del ácido 4-[(3-fluoro-5-trifluorometil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	499
147		Éster etílico del ácido 4-[(4-difluorometoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	479
148		Éster etílico del ácido 4-[(3-cloro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	447

149		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(3,4,5-trimetoxi-benzoilamino)-metil]-3,4-dihidro-2*H*-quinolin-1-carboxílico	503
150		Éster etílico del ácido 4-[(4-fluoro-3-metoxi- benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	461
151		Éster etílico del ácido 4-[(5-cloro-2-metil- benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	461
152		Éster etílico del ácido 4-[(3,5-dimetoxi-4-metil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	487
153		Éster etílico del ácido 4-[(2-cloro-3,4-dimetoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	507

154		Éster etílico del ácido 4-[(3-ciclopentiloxi-4-metoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	527
155		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-[(4-metoxi-3-propoxi-benzoilamino)-metil]-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	501
156		Éster etílico del ácido 4-[(2-cloro-4,5-dimetoxi-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	507
157		Éster etílico del ácido 6,7-dimetoxi-4-[(4-metoxi-3-metil-benzoilamino)-metil]-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	457
158		Éster etílico del ácido 4-{[(benzo[1,3]dioxol-5-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	457
159		Éster etílico del ácido 4-{[4-(1-terc-butoxicarbonil-pirrolidin-3-iloxi)-benzoilamino]-metil}-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	498

160		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-{[3-(2-oxo-pirrolidin-1-il)-benzoilamino]-metil}-3,4-dihidro-2*H*-quinolin-1-carboxílico	496
161		Éster etílico del ácido 4-{[3-(3,5-dimetil-pirazol-1-ilmetil)-benzoilamino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	521
162		Éster etílico del ácido 4-{[3-1-terc-butoxicarbonil-piperidin-4-il)-benzoilamino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	496
163		Éster etílico del ácido 4-{[(bifenil-3-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	489
164		Éster etílico del ácido 4-{[3',4'-dicloro-bifenil-4-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	557

165		Éster etílico del ácido 6,7-dimetoxi-2-metil-4-{[3-(5-metil-[1,2,4]oxadiazol-3-il)-benzoilamino]-metil}-3,4-dihidro-2*H*-quinolin-1-carboxílico	495
166		Éster etílico del ácido 4-{[3-(5-etil-[1,2,4]oxadiazol-3-il)-benzoilamino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	509
167		Éster etílico del ácido 4-{[(benzotiazol-6-carbonil)-amino]-metil}-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	470
168		Éster etílico del ácido 4-[(3-cloro-4-metil-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	461
169		Éster etílico del ácido 4-[(2-cloro-benzoilamino)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico	447

Preparación 34

3-Etil-6,7-dimetil-3,4-dihidro-1*H*-quinoxalin-2-ona

Una mezcla de 5,6-dimetil fenilendiamina (22,45 g, 165 mmol, 1 eq), ácido 2-cetobutírico (16,83 g, 165 mmol, 1 eq) y etanol (75 ml) se irradió en el microondas Milestone (Milestone Laboratories, Sorisole, Italia) durante 5 minutos a 180ºC. Después

de enfriarse, el sólido se filtró y se lavó con etanol. La concentración del filtrado y la cristalización posterior proporcionó la quinoxalin-2-ona deseada (18.45 g, 55,2%).

^{1}H RMN (dmso-d6: □ 1,17 (t, J = 7,05 Hz, 3H), 2,25 (s, 3H), 2,26 (s, 3H), 2,74 (q, J = 7,05 Hz, 2H), 7,00 (s, 1H), 7,48 (s, 1H), 12,15 (s a, 1H).

ESI-MS: 203 (MH+)

Preparación 35

3-Cloro-2-etil-6,7-dimetil-1,2-dihidro-quinoxalina

Una mezcla de 3-etil-6,7-dimetil-3,4-dihidro-1*H*-quinoxalin-2-ona (18,45 g, 91,2 mmol) se disolvió en 180 ml de oxicloruro fosforoso y la mezcla se calentó durante una noche a 110°C en un tubo de secado cargado con hidróxido de potasio y Drierite®. Después de enfriarse, el oxicloruro de fósforo (IV) se destiló cuidadosamente y el residuo se inactivó cuidadosamente con hielo, seguido de hidrogenocarbonato sódico saturado. La suspensión acuosa se extrajo varias veces con cloruro de metileno. Los materiales orgánicos combinados se lavaron 1 vez con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron para dar el compuesto del título (19,3 g, 81%) que se usó posteriormente sin purificación adicional.

^{1}H RMN (dmso-d6): □ 1,13 (t, J = 7,47 Hz, 3H), 3,04 (q, J = 7,47 Hz, 2H), 7,74 (s, 1H), 7,83 (s, 1H).

Preparación 36

2-Etil-6,7-dimetil-1,2,3,4-tetrahidro-quinoxalina

El residuo que contenía 3-cloro-2-etil-6,7-dimetil-1,2-dihidro-quinoxalina se disolvió en 200 ml de ácido acético y se añadieron 18.2 g de acetato sódico (222 mmol, 3 eq.). Después de aclarar con nitrógeno, el recipiente se cargó con paladio en carbono (10%, 7,86 g, 0,1 eq Pd, 7,39 mmol). La reacción se sometió a hidrogenación a 45 psi durante 5 horas después de las cuales cesó el desprendimiento del de hidrógeno. La

reacción se filtró a través de Celite® y se evaporó. El residuo se destiló azeotrópicamente 3 veces con heptano para retirar más ácido acético. Después, el residuo se repartió entre acetato de etilo e hidrogenocarbonato sódico acuoso saturado, 1 vez con salmuera, se secó sobre sulfato sódico anhidro, se filtró y se evaporó. La cromatografía ultrarrápida eluyendo con un gradiente de 20-50% acetato de etilo/hexanos proporcionó la quinoxalina deseada (10,56 g, rendimiento del 63%) en forma de sólido rosáceo mullido.

^{1}H RMN (dmso-d6): □ 0,89 (t, J = 7,46 Hz, 3H), 1,35 (m,2H), 1,89 (s, 3H), 1,94 (s, 3H), 2,75 (m, 1H), 2,96 (m, 1H), 3,14 (m, 1H), 6,12 (s, 1H), 6,17 (s, 1H).

Preparación 37

Éster terc-butílico del ácido 3-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Se disolvió 2-etil-6,7-dimetil-1,2,3,4-tetrahidro-quinoxalina (10,56 g, 55,6 mmol, 1 eq) en cloruro de metileno anhidro y se enfrió a -30ºC en un baño de etilenglicol/hielo seco. Se añadió gota a gota una solución de dicarbonato de terc-butilo (12,3 g, 55,6 mmol, 1 eq) en cloruro de metileno (50 ml) y la reacción se dejó calentar lentamente a temperatura ambiente durante una noche. La reacción se evaporó a sequedad y se repartió entre acetato de etilo y HCl 0,1M. La capa orgánica se lavó 3 veces con HCl 0,1M, 1 vez con hidrogenocarbonato sódico saturado, 1 vez con salmuera, se secó sobre sulfato sódico anhidro, se filtró y se evaporó. La cromatografía en sílice eluyendo con 10% acetato de etilo/hexano proporcionó el compuesto deseado (10,35 g, 64%)

^{1}H RMN (dmso-d6): □ 0,90 (t, J = 7,47 Hz, 3H), 1,34 (m,2H), 1,41 (s, 9H), 2,02 (s, 6H), 3,09 (m, 1H), 3,24 (m, 1H), 3,58 (m, 1H), 5,74 (s, 1H), 6,34 (s, 1H), 7,05 (s a, 1H).

ESI-MS: 290 (M+), 235 (MH+ - isobutileno).

Preparación 38

Éster 1-etílico, éster terc-butílico del ácido 2-etil-6,7-dimetil-2,3-dihidro-quinoxalin-1,4-dicarboxílico

Una solución de éster terc-butílico del ácido 3-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (10,35 g, 35,7 mmol, 1 eq) y 4-dimetilaminopiridina (436 mg, 3,57 mmol, 0,1 eq) en piridina anhidro (250 ml) se enfrió a 0°C y se añadió gota a gota cloroformiato de etilo (17,0 ml, 178,3 mmol, 5 eq). La reacción se dejó calentar a temperatura ambiente durante una noche. Los disolventes se destilaron azeotrópicamente 3 veces con heptanos. El residuo, después de secar al vacío, se repartió entre acetato de etilo y HCl 0,1M. La capa orgánica se lavó con HCl 0,1M hasta que los extractos eran ácidos, después se lavó 1 vez con hidrogenocarbonato sódico saturado, 1 vez con agua, 1 vez con salmuera. La capa orgánica se secó sobre sulfato sódico anhidro, se filtró y se evaporó para proporcionar el compuesto deseado (100%)

^{1}H RMN (dmso-d6): □ 0,77 (t, J = 7,05 Hz, 3H), 1,20 (t, J = 7,05 Hz, 3H), 1,25 (m, 2H), 1,44 (s, 9H), 2,13 (s, 6H), 3,55 (dd, J = 13,35, 4,98 Hz, 1H), 3,78 (dd, J = 13,1 3,32 Hz, 1H), 4,12 (m, 2H), 4,39 (m, 1H), 7,41 (s, 1H), 7,44 (s, 1H).

ESI-MS: 307 (MH+ - isobutileno), 263 (MH +- boc).

Preparación 39

Éster etílico del ácido 2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

A éster 1-etílico, éster terc-butílico del ácido 2-etil-6,7-dimetil-2,3-dihidro-quinoxalin-1,4-dicarboxílico (12,93 g) se le añadió ácido trifluoroacético (200 ml), la mezcla se agitó hasta que se formó una solución y después se evaporó a sequedad al vacío. El residuo se destiló azeotrópicamente 3 veces con heptano y se secó al vacío. Después, el aceite residual se repartió entre cloruro de metileno y bicarbonato sódico acuoso saturado. La capa acuosa se extrajo 3 veces con cloruro de metileno. Los

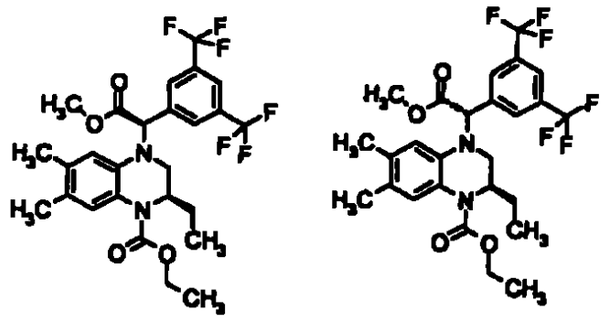
extractos combinados de cloruro de metileno se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron, dando la quinoxalina deseada (100%).

^{1}H RMN (dmso-d6): □ 0,77 (t, J = 7,47 Hz, 3H), 1,19 (t, J = 7,05 Hz, 3H), 1,24 (m, 2H), 2,02 (s, 6H), 3,14 (m, 2H), 4,08 (m, 2H), 4,24 (m, 1H), 5,72 (m, 1H), 7,11 (s a, 1H).

ESI-MS: 263 (MH+).

Esta quinoxalina racémica se sometió a separaciones quirales preparativas usando una columna quiral preparativa Chiralcel OD 10x25 cm. El eluyente fue etanol al 5% en heptano, con un caudal de 275 ml/min, observando a 300 nm. La muestra se cargó en la columna usando 2:1 metanol/diclorometano. El tiempo de retención del enantiómero S fue de 16 minutos, el del enantiómero R de 22 min. Una muestra de 26 g se sometió a estas condiciones, dando como resultado 10 g del enantiómero R, 99,4% ee y 11 g del enantiómero S, 95,1% ee.

Ejemplos 170, 171, 172 y 173



Éster etílico del ácido (*R,R, R,S, S,R* y *S,S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Procedimiento A: Una mezcla de éster etílico de ácido (*RS*)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (652 mg, 1 eq, 2,5 mmol), éster metílico del ácido bromo-4-(3,5-bis-trifluorometil-fenil)-acético (1,0 g, 1,1 eq, 2,74 mmol) y 2,6-

lutidina (0,87 ml, 3 eq, 7,47 mmol) en dimetilformamida (3 ml) se calentó a 140°C durante 20 minutos por irradiación de microondas en un Emrys Optimizer (Personal Chemistry, Uppsala, Suecia). La mezcla se repartió entre cloruro de metileno y agua y las fases se separaron. La fase acuosa se extrajo 3 veces con cloruro de metileno y los extractos orgánicos combinados se lavaron 2 veces con agua, 1 vez con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron. La cromatografía en gel de sílice usando acetato de etilo al 10% en hexanos como eluyente proporcionó los compuestos del título en forma de mezcla de dos diastereoisómeros (900 mg, 66%).

Procedimiento B: Una mezcla de éster etílico de ácido (*RS*)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (652 mg, 1 eq, 2,5 mmol), éster metílico del ácido bromo-4-(3,5-bis-trifluorometil-fenil)-acético (1,0 g, 1,1 eq, 2,74 mmol) y 2,6-lutidina (0,87 ml, 3 eq, 7,47 mmol) en dimetilformamida (3 ml) se agitó a temperatura ambiente durante 24 horas. La mezcla se repartió entre cloruro de metileno y agua y las fases se separaron. La fase acuosa se extrajo 3 veces con cloruro de metileno y los extractos orgánicos combinados se lavaron 2 veces con agua, 1 vez con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron. La cromatografía en gel de sílice usando acetato de etilo al 10% en hexanos como eluyente proporcionó los compuestos del título en forma de mezcla de dos diastereoisómeros (900 mg, 66%).

Diastereoisómero 1 ^{1}H RMN ($CDCl_3$): □ 0,71 (t, J = 7,5 Hz, 3H), 1,30 (t, J = 7,05 Hz, 3H), 1,46 (m, 2H), 2,18 (s, 3H), 2,20 (s, 3H), 2,77 (dd, J = 9,54, 2,08 Hz, 1H), 3,37 (dd, J = 11,38, 3,32 Hz, 1H), 3,82 (s, 3H), 4,20 (m, 2H), 4,26 (m, 1H), 5,82 (s, 1H), 6,58 (s, 1H), 7,49 (s a, 1H), 7,75 (s, 2H), 7,88 (s, 1H).

LCMS (ESI+): 547 (MH+).

Diastereoisómero 2: ^{1}H RMN ($CDCl_3$): □ 0,87 (t, J = 7,47 Hz, 3H), 1,28 (t, J = 6,64 Hz, 3H), 1,43 (m, 2H), 2,18 (s, 3H), 3,11 (dd, J = 11,35, 4,98 Hz, 1H), 3,22 (dd, J

= 10,79, 1,66 Hz, 1H), 3,83 (s, 3H), 4,19 (m, 2H), 4,44 (m, 1H), 5,66 (s,1H), 6,41 (s, 1H), 7,28 (s a, 1H), 7,73 (s, 2H), 7,86 (s, 1H).

LCMS (ESI+): 547 (MH+).

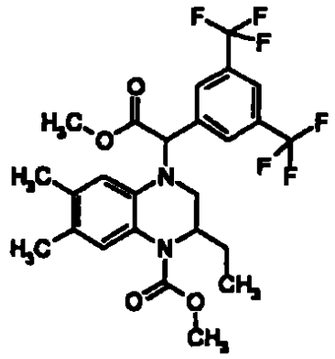
Este mezcla racémica de diastereisómeros se resolvió adicionalmente por HPLC quiral en una columna Pirkle Covalent (S,S)Whelk-O 1 (Regis Techonologies, Inc., Morton Grove, IL) (5 x 25 cm) eluyendo a 100 ml/min con etanol al 5%/heptano para proporcionar tres fracciones:

Isómero 1, tiempo de retención = 18 minutos

Isómeros 2 y 3, tiempo de retención = 25 minutos

Isómero 4, tiempo de retención = 37 minutos

Ejemplos 174 y 175



Preparación del éster metílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Este compuesto se preparó usando el procedimiento descrito anteriormente para el éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico, pero usando cloroformiato de metilo en lugar de cloroformiato de etilo.

Diastereoisómero 1 ^{1}H RMN ($CDCl_3$): □ 0,86 (t, J = 7,47 Hz, 3H), 1,43 (m, 2H),

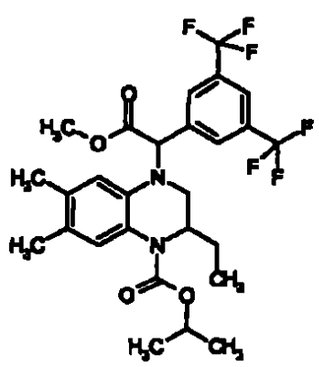
2,18 (s, 6H), 3,10 (dd, J = 11,48, 4,98 Hz, 1H), 3,22 (dd, J = 11,17 Hz, 1,66 Hz, 1H), 3,75 (s, 3H), 4,43 (m, 1H), 3,82 (s, 3H), 55,66 (s, 1H), 6,41 (s, 1H), 7,22 (s a, 1H), 7,72 s, 2H), 7,86 (s, 1H).

LCMS (ESI+): 532 (MH+).

Diastereoisómero 2: ^{1}H RMN ($CDCl_3$): □ 0,71 (t, J = 7,47 Hz, 3H), 1,19 (m, 1H), 1,43 (m, 1H), 2,19 (s, 3H), 2,20 (s, 3H), 2,77 (dd, J = 11,47, 1,65 Hz, 1H), 3,38 (dd, J = 11,30, 3,74 Hz, 1H), 3,77 (s, 3H), 3,81 (s, 3H), 4,38 (m, 1H), 5,83 (s, 1H), 6,58 (s, 1H), 7,37 (s, 1H), 7,75 (s, 2H), 7,88 (s, 1H).

LCMS (ESI+): 532 (MH+).

Ejemplos 176 y 177



Preparación del éster isopropílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Este compuesto se preparó usando el procedimiento descrito anteriormente para el éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico, pero usando cloroformiato de isopropilo en lugar de cloroformiato de etilo.

Diastereoisómero 1 ^{1}H RMN ($CDCl_3$): □ 0,86 (t, J = 7,47 Hz, 3H), 1,16 (dd, J = 6,22, 6,22 Hz, 3H), 1,26 (dd, J = 15,07, 6,22 Hz, 3H), 1,50 (m, 2H), 2,17 (s, 6H), 3,10

(m, 1H), 3,2 (m, 1H), 3,82 (s, 3H), 4,42 (m, 1H), 5,00 (m, 1H), 5,65 (s, 1H), 6,40 (s,1 H), 7,31 (s a, 1H), 7,64 (s, 1H), 7,74 (s, 1H).

LCMS (ESI+): 560 (MH+).

Diastereoisómero 2: ^{1}H RMN ($CDCl_3$): □ 0,71 (t, J = 7,47 Hz, 3H), 1,16 (m, 1H), 1,26 (d, J = 6,23 Hz), 1,29 (d, J = 5,81 Hz), 1,44 (m, 1H), 2,18 (s, 3H), 2,20 (s, 3H), 2,76 (dd, J = 11,52, 2,07 Hz, 1H), 3,37 (dd, J = 11,52, 3,32 Hz), 3,82 (s, 2H), 4,38 (m, 1H), 5,01 (m, 1H), 5,82 (s, 1H), 6,58 (s, 1H), 7,47 (s a, 1H), 7,75 (s, 2H), 7,88 (s, 1H).

LCMS (ESI+): 561 (MH+).

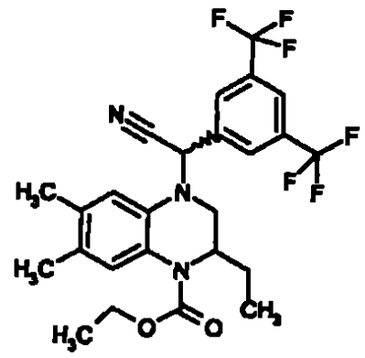
Preparación 40

(3,5-bis-trifluorometil-fenil)-bromo-acetonitrilo

A una solución de (3,5-bis-trifluorometil-fenil)-bromo-acetonitrilo (2,0 g, 7,9 mmol) en tetracloruro de carbono (20 ml) se le añadió peróxido de dibenzoílo (0,076 g, 0,3 mmol) y N-bromosuccinimida (1,4 g, 7,9 mmol). Esta mezcla de reacción se calentó a reflujo durante 24 horas, después se diluyó con cloruro de metileno y se lavó con salmuera. La capa orgánica se secó y se concentró para dar el producto bruto que se purificó por cromatografía en gel de sílice usando acetato de etilo al 2% en hexanos como eluyente para proporcionar el compuesto del título (2,0 g, 75%).

LCMS (ESI+): 333 (MH+)

Ejemplo 178



Éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

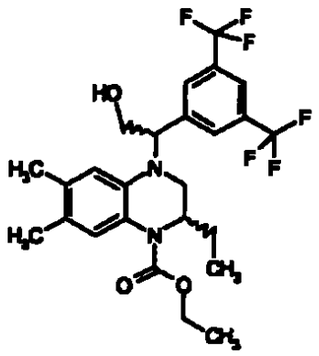
Procedimiento A: Una mezcla de éster etílico de ácido 2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (1 g, 1 eq, 3,81 mmol), éster metílico del ácido 3,5-bis-(trifluorometil-fenil)-bromo-acetonitrilo (Preparación 40, 1,27 g, 1 eq, 3,81 mmol) y carbonato de potasio (1,58 g, 3 eq, 11,43 mmol) en acetonitrilo (5 ml) se sometió a irradiación en microondas en un Emrys Optimizer (Personal Chemistry, Uppsala, Suecia) a 140°C durante 20 minutos. La mezcla se repartió entre cloruro de metileno y agua y las fases se separaron. La fase acuosa se extrajo 3 veces con cloruro de metileno y los extractos orgánicos combinados se lavaron 2 veces con agua, 1 vez con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron. La cromatografía en gel de sílice usando un gradiente de 10-30% de acetato de etilo en hexanos como eluyente proporcionó los compuestos del título en forma de mezcla de dos diastereoisómeros (1,5:1) (900 mg, 29%).

Procedimiento B: Una mezcla de éster etílico de ácido 2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (1 g, 1 eq, 3,81 mmol), éster metílico del ácido 3,5-bis-(trifluorometil-fenil)-bromo-acetonitrilo (Preparación 40, 1,27 g, 1 eq, 3,81 mmol) y 2,6-lutidina (3 eq, 11,43 mmol) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 24 horas. La mezcla se repartió entre cloruro de metileno

y agua y las fases se separaron. La fase acuosa se extrajo 3 veces con acetato de etilo y los extractos orgánicos combinados se lavaron 2 veces con agua, 1 vez con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron. La cromatografía en gel de sílice usando un gradiente de 10-30% de acetato de etilo en hexanos como eluyente proporcionó el nitrilo deseado en forma de mezcla de dos diastereoisómeros (1,5:1) (900 mg, 29%).

LCMS (ESI+): 514 (MH+).

Ejemplo 179



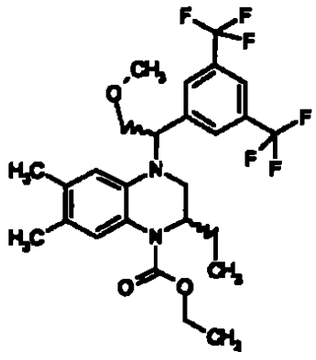
Preparación del éster etílico del ácido 4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

A una solución del éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (0,14 g, 0,26 mmol) en tetrahidrofurano (5 ml) a -78°C se le añadió gota a gota una solución de hidruro de aluminio litio (1M en tetrahidrofurano 0,16 ml). Esta solución se calentó lentamente a temperatura ambiente durante 3 horas. La mezcla de reacción se inactivó con sulfato sódico hexahidrato (3 g) y la mezcla se agitó durante 30 minutos. La mezcla de reacción se filtró y se concentró para producir el producto en bruto (mezcla de diastereoisómeros) que se purificó por cromatografía en gel de sílice eluyendo con acetato de etilo al 10% en hexanos para dar el compuesto del título (0,08 g, 70%).

^{1}H RMN ($CDCl_3$): □ 0,71 (t, J = 7,57 Hz, 3H), 0,965 (t, J = 7,05 Hz, 3H), 1,26 (m, 2H), 2,20 (s a, 6H), 2,97 (dd, 1H), 3,25 (m, 1H), 3,37 (m, 1H), 3,85 (m, 2H), 4,15 (m, 3H), 4,5 (m a, 1H), 4,62 (m, 1H), 4,70 (m, 1H), 5,82 /s, 1H), 6,58 (s, 1H), 7,49 (s a, 1H), 7,75 (s, 2H), 7,88 (s, 1H).

LCMS (ESI+): 518 (MH+)

Ejemplo 180



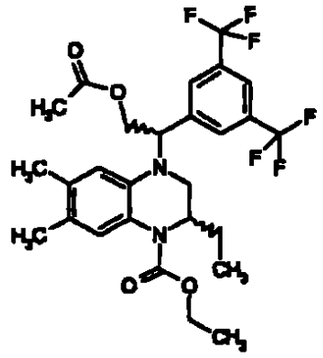
Preparación del éster etílico del ácido 4-[1-(3,5-bis-trifluorometil-fenil)-2-metoxi-etil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

A una solución del éster etílico del ácido 4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (0,044 g, 0,13 mmol) en dimetilformamida anhidro (93 ml) se le añadió hidruro sódico (suspensión al 60%, 0,005 g, 0,27 mmol) y la mezcla se agitó durante 20 minutos. Se añadió un exceso de yoduro de metilo y la reacción se agitó durante 1 hora y se inactivó con cloruro de amonio saturado. La mezcla se extrajo con éter (3x20 ml) y se concentró. La cromatografía en gel de sílice del producto en bruto usando un gradiente de acetato de etilo 10-30% en hexanos como eluyente proporcionó el producto deseado en forma de un aceite (0,015 g, 35%).

^{1}H RMN ($CDCl_3$): □ 0,71 (t, J = 7,57 Hz, 3H), 1,30 (t, J = 7,05 Hz, 3H), 1,46 (m, 2H), 2,20 (s a, 6H), 2,97 (dd, 1H), 3,25 (m, 1H), 3,37 (m, 1H), 3,4 (s, 3H), 3,85 (m, 2H), 4,26 (m, 1H), 4,5 (m a, 1H), 4,62 (m, 1H), 4,70 (m, 1H), 5,82 (s, 1H), 6,58 (s, 1H), 7,49 (s a, 1H), 7,75 (s, 2H), 7,88 (s, 1H).

LCMS (ESI+): 532 (MH+).

Ejemplo 181



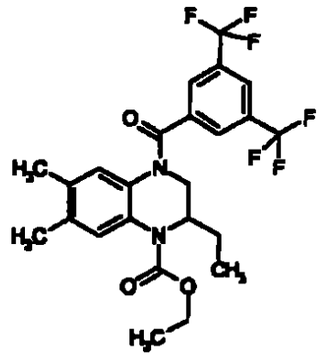
Preparación del éster etílico del ácido 4-[2-acetoxi-1-(3,5-bis-trifluorometil-fenil)-etil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Se disolvió éster etílico del ácido 4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico en una mezcla 1:1 de anhídrido acético y piridina (4 ml) y la mezcla se agitó a temperatura ambiente durante 10 horas. El disolvente se retiró al vacío y el residuo se purificó por cromatografía en gel de sílice para producir el acetato deseado (25 mg, 58%; mezcla de diastereoisómeros).

^{1}H RMN ($CDCl_3$): □ 0,71 (t, J = 7,57 Hz, 3H), 1,30 (t, J = 7,05 Hz, 3H), 1,46 (m, 2H), 1,98 (s, 3H), 2,18 (s, 3H), 2,20 (s, 3H), 2,77 (d, 1H), 3,05 (m, 1H), 3,37 (m, 1H), 4,20 (m, 2H), 4,26 (m, 1H), 4,5 (m, 1H), 4,62 (m, 1H), 4,70 (m, 1H), 5,82 (s, 1H), 6,58 (s, 1H), 7,49 (s a, 1H), 7,75 (s, 2H), 7,88 (s, 1H).

LCMS (ESI+): 560 (MH+)

Ejemplo 182



Preparación del éster etílico del ácido 4- (3,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Una solución a temperatura ambiente de éster etílico del ácido 2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (0,1 g, 1 eq, 0,38 mmol) en 5 ml de cloruro de metileno se trató con el cloruro ácido formado por combinación de ácido 3,5-bis-(trifluorometil)benzoico (147 mg, 1,5 eq, 0,57 mmol), cloruro de oxalilo (0,05 ml, 1,5 eq, 0,57 mmol) y una gota de dimetilformamida anhidro. La reacción se dejó calentar durante una noche a temperatura ambiente, después de lo cual la reacción se inactivó con hidrogenocarbonato sódico saturado y se extrajo con 3 veces con cloruro de metileno. Los extractos orgánicos combinados se lavaron 1 vez con HCl 1M, 1 vez con hidrogenocarbonato sódico saturado, 1 vez con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron. La cromatografía en gel de sílice usando un gradiente de 10-20% de acetato de etilo en hexanos como eluyente proporcionó éster etílico del ácido 4- (3,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (130 mg, 68%).

^{1}H RMN ($CDCl_3$): □ 0,91 (t, J = 7,47 Hz, 3H), 1,30 (t, J = 7,04 Hz, 3H), 1,50 (m, 1H), 1,60 (m, 1H), 1,94 (s, 3H), 2,20 (s, 3H), 3,39 (m, 1H), 4,26 (q, J = 6,22 Hz, 2H), 4,68 (m, 2H), 6,29 (s a, 1H), 7,41 (s a, 1H), 7,78 (s, 2H), 7,85 (s, 1H).

FIA-MS (APCI+): 503 (MH+).

Preparación 41

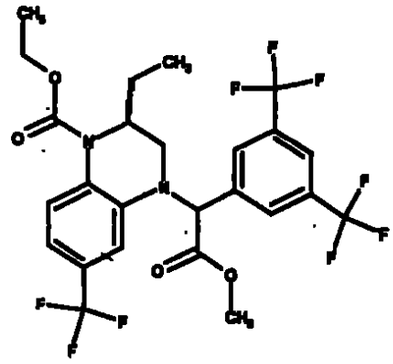
6-Trifluorometil-1,2,3,4-tetrahidro-quinoxalina

La quinoxalina deseada se preparó usando el procedimiento descrito por V. Krchnak *et al.*, (*Tetrahedron Lett. 42*, 2443-2446 (2001)) usando 3-(*R*)-amino-pentan-1-ol y 2-fluoro-5-trifluorometil-nitrobenceno.

^{1}H RMN (dmso-d6): □ 1,06 (t, J = 7,48 Hz, 3H), 1,73 (m, J = 7,90 Hz, 2H), 3,19 (dd, J = 9,96 Hz, 1H), 3,68 (dd, J = 9,55 Hz, 1H), 3,71 (m, 1H), 6,98 (d, J = 8,3 Hz, 1H), 7,25 (dd, 1H), 7,43 (s, 1H).

ESI-MS: 231 (MH+).

Ejemplo 183



Éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Una solución de la 6-trifluorometil-1,2,3,4-tetrahidro-quinoxalina (Preparación 41, 0,01 g, 0,04 mmol, 1 eq), bromuro de 3,5-bis-trifluorometil-fenil)metoxicarbonil-metilo (0,017 g, 0,044 mmol, 1,1 eq) y 2,6-lutidina (0,014 g, 0,12 mmol, 3 eq) en dimetilformamida (0,5 ml) se irradió en el microondas Milestone (Milestone Laboratories, Sorisole, Italia) durante 10 minutos a 140°C. El disolvente se retiró a presión reducida para producir un aceite oscuro que se usó sin purificación adicional.

ESI-MS: 542 (MH^+).

Este residuo se combinó con 2,6-lutidina (0,018 g, 0,16 mmol, 2 eq.) y cloroformiato de etilo (0,0175 g, 0,16 mmol, 2 eq) en dimetilformamida (0,5 ml) y se calentó a 140°C durante 10 minutos por irradiación en un microondas Milestone (Milestone Laboratories, Sorisole, Italia). La solución se purificó por HPLC preparativa eluyendo con NH_4OH acuoso al 0,1%, 70-0% con acetonitrilo, NH_4OH al 0,1%, duración del gradiente 6 minutos y 8 minutos de tiempo de realización para producir el compuesto del título.

ESI-MS: 587 (MH+).

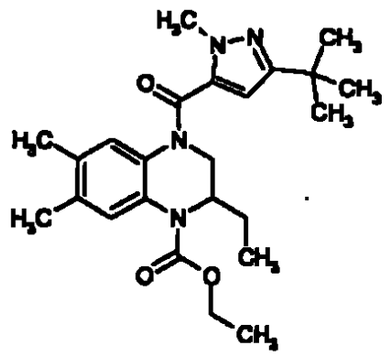
Procedimiento general para la síntesis paralela de amidas:

Los ácidos benzoicos necesarios (0,06 mmol, 1 eq) se combinaron con PS-PPh_3 (115 mg, 1,51 mmol/g, 3 eq, 0,18 mmol) (Argonaut Technologies, Inc., Foster City, CA) en viales de 2 dracmas cerrados y separados mediante un tabique. A esta mezcla sólida se le añadió dicloroetano (1 ml) mediante un manipulador de líquidos Tecan US (Research Triangle Park, NC). A esta suspensión se le añadió mediante el Tecan una solución de tricloroacetonitrilo (0,0072 ml, 1,2 eq, 0,07 mmol) en dicloroetano (1 ml) y las reacciones se agitaron levemente por medio de un agitador orbital durante 3 horas. A esta solución se le añadió PS-DIPAM (56 mg, 3,2 mmol/g, 3 eq, 0,18 mmol) (Polymer Laboratories, Amherst, MA) y se añadió una solución de éter 2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalin-1-carboxílico (15 mg, 0,06 mmol, 1,0 eq) en dicloroetano (1 ml) con el Tecan. Las reacciones se agitaron durante una noche. Las reacciones se filtraron a través de tubos de filtrado usando el manipulador de líquidos Tecan y las resinas se lavaron 3 veces con dicloroetano. Las soluciones se evaporaron usando un evaporador por centrifugación Genevac Mega660 (Genevac Ltd., Suffolk, UK) y los residuos se redisolvieron en dimetilsulfóxido (0,2 ml) y se purificaron usando el sistema de HPLC

preparativa de Shimadzu (Shimadzu Corporation, Kyoto, Japón) eluyendo con un gradiente de 80-100% de acetonitrilo/agua/ácido fórmico al 0,1% en una columna 19x50 mm Waters Symettry (Waters Corp, Milford, MA) durante 8 minutos, tiempo de gradiente 6 minutos, 25 ml/min, recogida provocada por UV, con observancia a 210 nm. Las fracciones que contenían el producto se evaporaron a sequedad usando el evaporador por centrifugación Genevac Mega660 (Genevac Ltd., Suffolk, UK).

Usando los materiales de partida apropiados, se prepararon los Ejemplos 184-409 en forma de mezclas racémicas de manera análoga al Ejemplo 183:

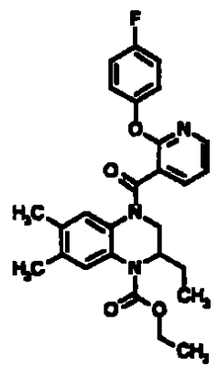
Ejemplo 184



Éster etílico del ácido 4-[5-terc-butil-2-metil-2*H*-pirazol-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

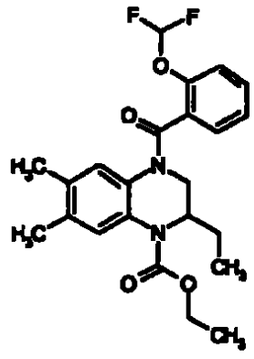
Ejemplo 185



Éster etílico del ácido 2-etil-4-[2-(4-fluoro-fenoxi-piridin-3-carbonil]-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): (MH+).

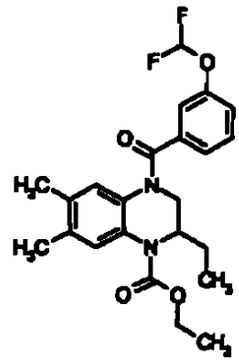
Ejemplo 186



Éster etílico del ácido 4-(2-difluorometoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 478 (MH+).

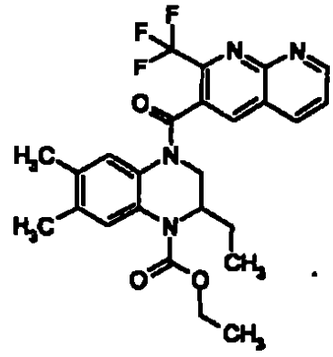
Ejemplo 187



Éster etílico del ácido 4-(3-difluorometoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 433 (MH+).

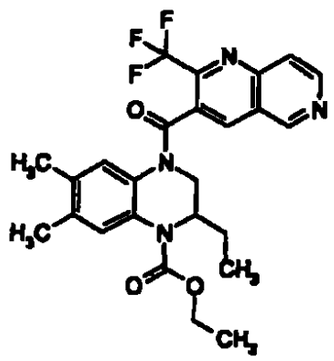
Ejemplo 188



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-trifluorometil-[1,8]naftiridin-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 487 (MH+).

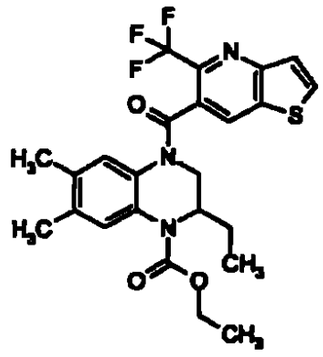
Ejemplo 189



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-trifluorometil-[1,6]naftiridin-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 487 (MH+).

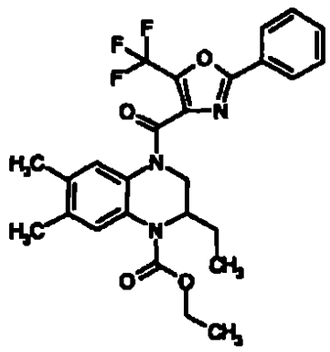
Ejemplo 190



Éster etílico del ácido 2-etil-4-(5-trifluorometil-tieno[3,2-b]piridin-6-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 492 (MH+).

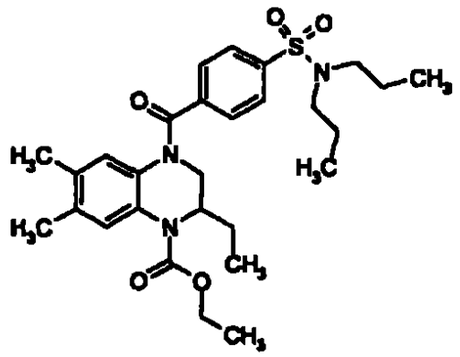
Ejemplo 191



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-fenil-5-trifluorometil-oxazol-4-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 502 (MH+).

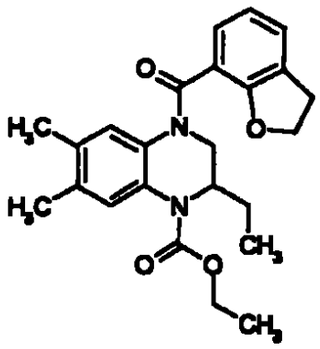
Ejemplo 192



Éster etílico del ácido 4-(4-dipropilsulfamoil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 530 (MH+).

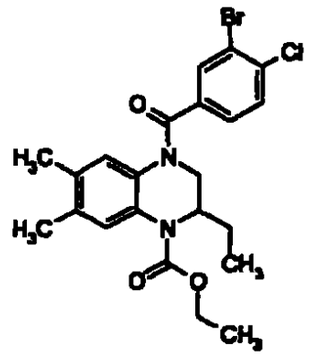
Ejemplo 193



Éster etílico del ácido 4-(2,3-dihidro-benzofuran-7-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 409 (MH+).

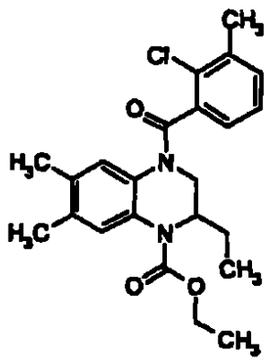
Ejemplo 194



Éster etílico del ácido 4-(3-bromo-4-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 480 (MH+).

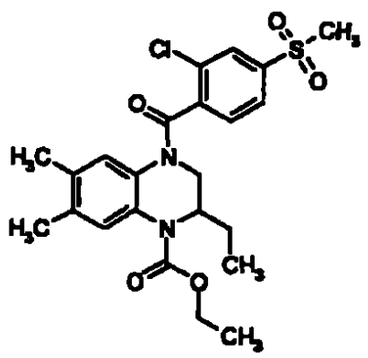
Ejemplo 195



Éster etílico del ácido 4-(2-cloro-3-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 415 (MH+).

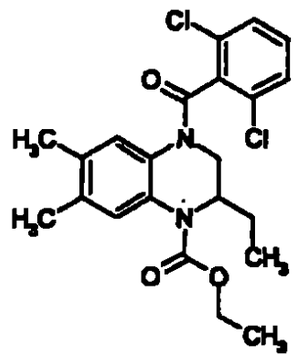
Ejemplo 196



Éster etílico del ácido 4-(2-cloro-4-metanosulfonil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 479 (MH+).

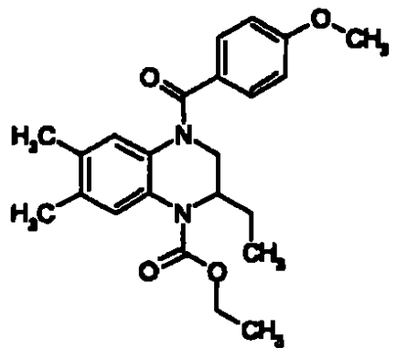
Ejemplo 197



Éster etílico del ácido 4-(2,6-dicloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 436 (MH+).

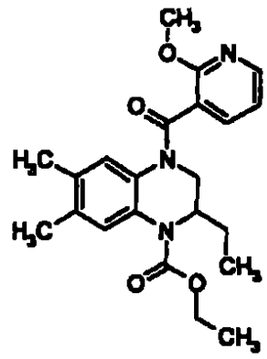
Ejemplo 198



Éster etílico del ácido 2-etil-4-(4-metoxi-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 397 (MH+).

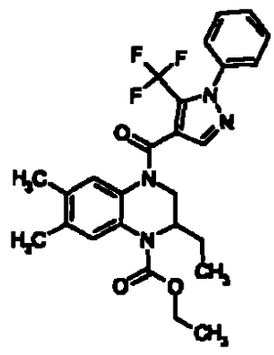
Ejemplo 199



Éster etílico del ácido 2-etil-4-(2-metoxi-piridin-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 398 (MH+).

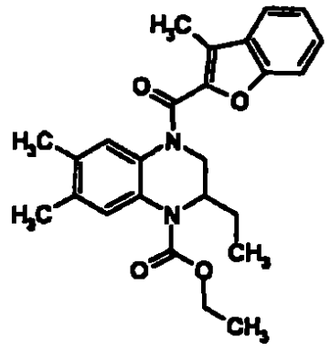
Ejemplo 200



Éster etílico del ácido 2-etil-6,7-dimetil-4-(1-fenil-5-trifluorometil-1H-pirazol-4-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 501 (MH+).

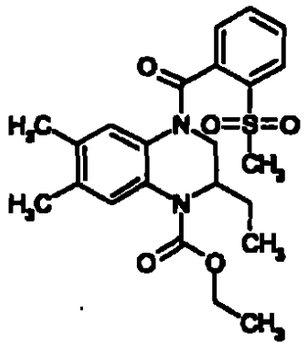
Ejemplo 201



Éster etílico del ácido 2-etil-6,7-dimetil-4-(3-metil-benzofuran-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 421 (MH+).

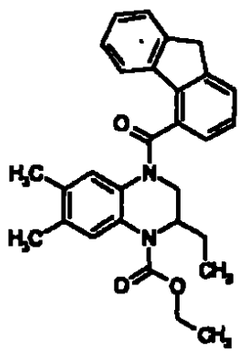
Ejemplo 202



Éster etílico del ácido 2-etil-4-(2-metanosulfonil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 445 (MH+).

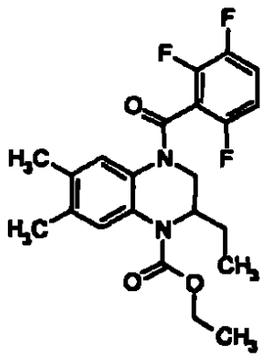
Ejemplo 203



Éster etílico del ácido 2-etil-4-(9H-fluoreno-4-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 455 (MH+).

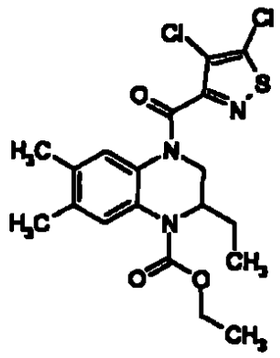
Ejemplo 204



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2,3,6-trifluoro-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 421 (MH+).

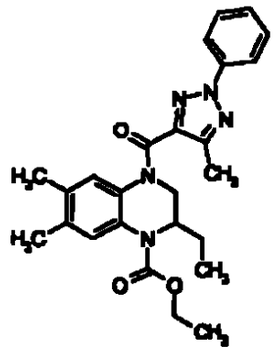
Ejemplo 205



Éster etílico del ácido 4-(4,5-dicloro-isotiazol-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 443 (MH+).

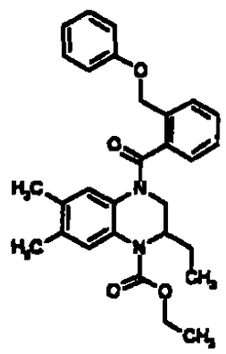
Ejemplo 206



Éster etílico del ácido 2-etil-6,7-dimetil-4-(5-metil-2-fenil-2H[1,2,3]triazol-4-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 448 (MH+).

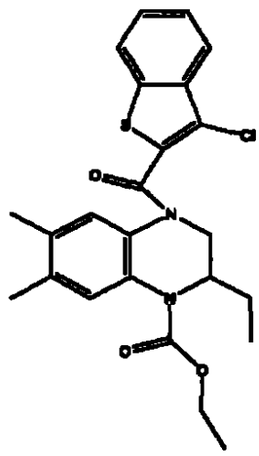
Ejemplo 207



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-fenoximetil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 473 (MH+).

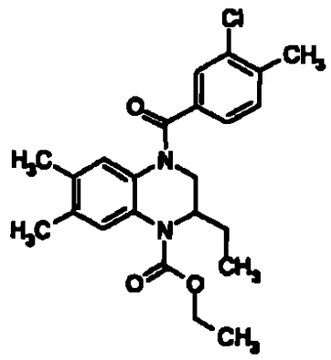
Ejemplo 208



Éster etílico del ácido 4-(3-cloro-benzo[b]tiofeno-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 457 (MH+).

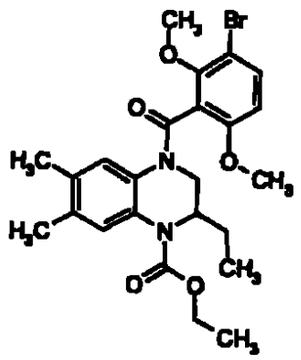
Ejemplo 209



Éster etílico del ácido 4-(3-cloro-4-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 415 (MH+).

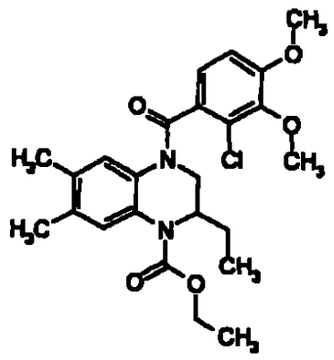
Ejemplo 210



Éster etílico del ácido 4-(3-bromo-2,6-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 506 (MH+).

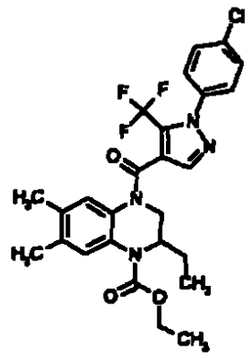
Ejemplo 211



Éster etílico del ácido 4-(2-cloro-3,4-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

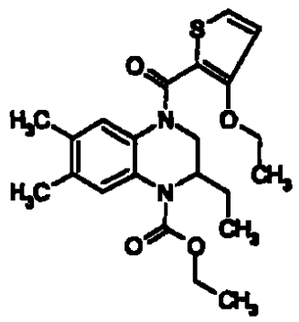
Ejemplo 212



Éster etílico del ácido 4-[1-(4-cloro-fenil)-5-trifluorometil-1*H*-pirazol-4-carbonil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 535 (MH+).

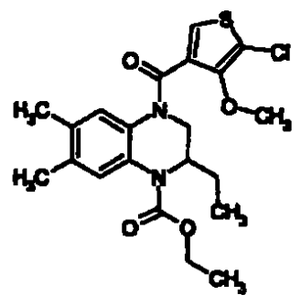
Ejemplo 213



Éster etílico del ácido 4-(3-etoxi-tiofeno-2-carbonil)-2-etil- 6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 417 (MH+).

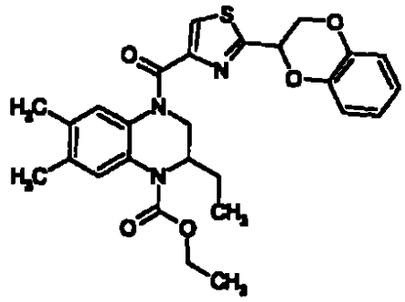
Ejemplo 214



Éster etílico del ácido 4-(5-cloro-4-metoxi-tiofeno-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 437 (MH+).

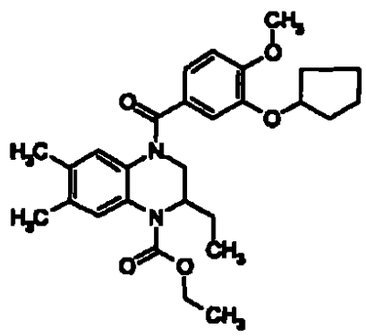
Ejemplo 215



Éster etílico del ácido 4-[2-(2,3-dihidro-benzo[1,4]dioxin-2-il)-tiazol-4-carbonil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 508 (MH+).

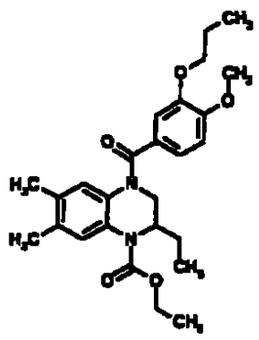
Ejemplo 216



Éster etílico del ácido 4-(3-ciclopentil-4-metoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 481 (MH+).

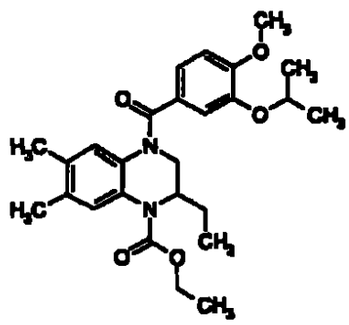
Ejemplo 217



Éster etílico del ácido 2-etil-4-(4-metoxi-3-propoxi-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 455 (MH+).

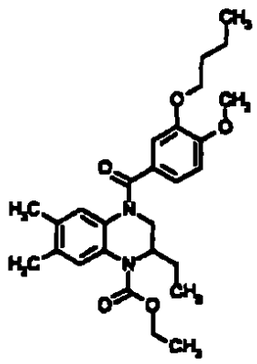
Ejemplo 218



Éster etílico del ácido 2-etil-4-(3-isopropoxi-4-metoxi-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 455 (MH+).

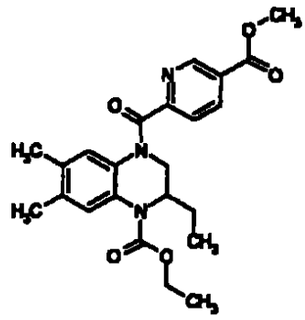
Ejemplo 219



Éster etílico del ácido 4-(3-butoxi-4-metoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 469 (MH+).

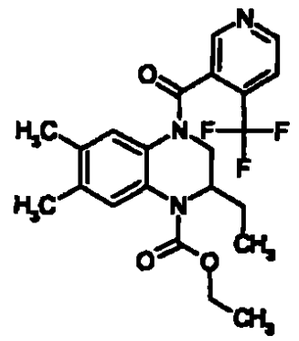
Ejemplo 220



Éster etílico del ácido 2-etil-4-(5-metoxicarbonil-piridin-2-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 426 (MH+).

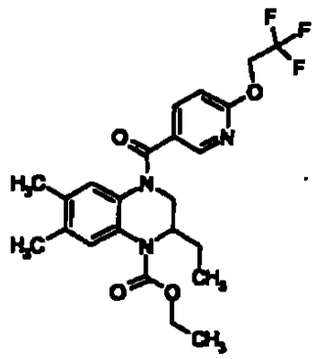
Ejemplo 221



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-trifluorometil-piridin-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 436 (MH+).

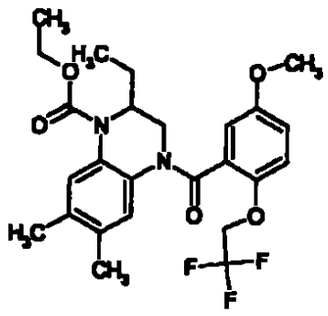
Ejemplo 222



Éster etílico del ácido 2-etil-6,7-dimetil-4-[6-(2,2,2-trifluoro-etoxi)-piridin-3-carbonil]-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 466 (MH+).

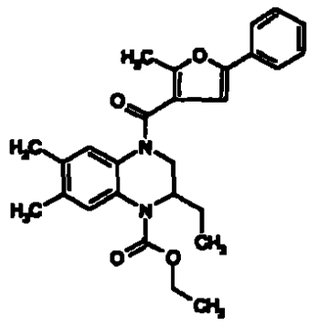
Ejemplo 223



Éster etílico del ácido 2-etil-4-[5-metoxi-2-(2,2,2-trifluoro-etoxi)-benzoil]-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 495 (MH+).

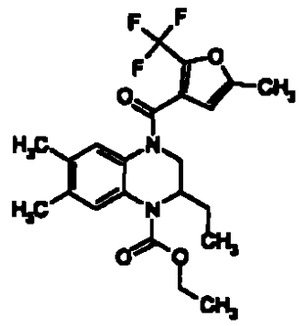
Ejemplo 224



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-metil-5-fenil-furan-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 447 (MH+).

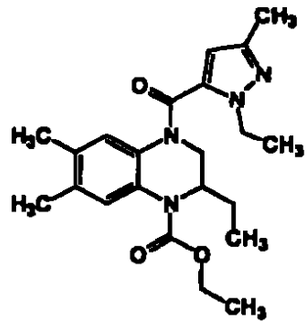
Ejemplo 225



Éster etílico del ácido 2-etil-6,7-dimetil-4-(5-metil-2-trifluorometil-furan-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 439 (MH+).

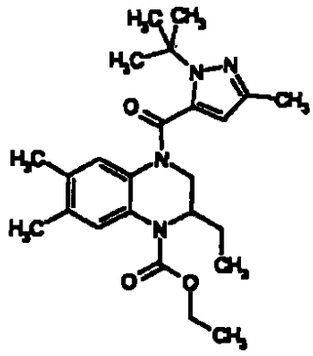
Ejemplo 226



Éster etílico del ácido 2-etil-4-(2-etil-5-metil-2*H*-pirazol-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 399 (MH+).

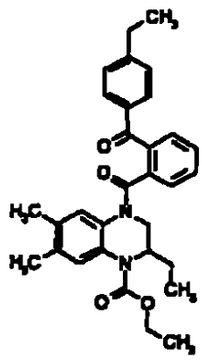
Ejemplo 227



Éster etílico del ácido 4-(2-terc-butil-5-metil-2*H*-pirazol-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

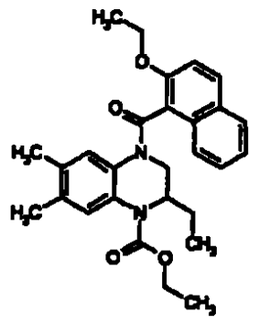
Ejemplo 228



Éster etílico del ácido 2-etil-4-[2-(4-etil-benzoil)-benzoil]-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 499 (MH+).

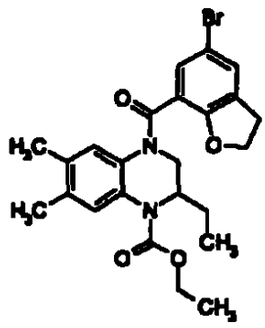
Ejemplo 229



Éster etílico del ácido 4-[2-etoxi-naftalen-1-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

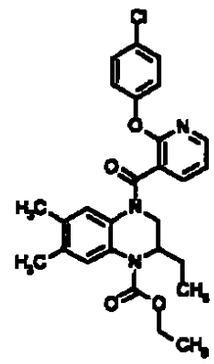
Ejemplo 230



Éster etílico del ácido 4-(5-bromo-2,3-dihidro-benzofuran-7-carbonil)- 2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 488 (MH+).

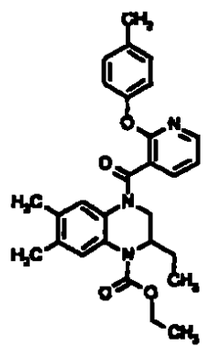
Ejemplo 231



Éster etílico del ácido 4-[2-(4-cloro-fenoxi)-piridin-3-carbonil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 494 (MH+).

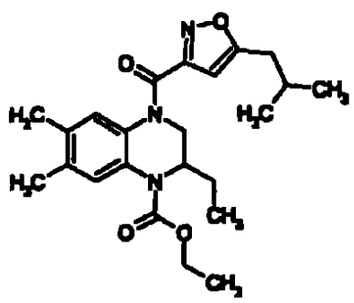
Ejemplo 232



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-p-toliloxi-piridin-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 474 (MH+).

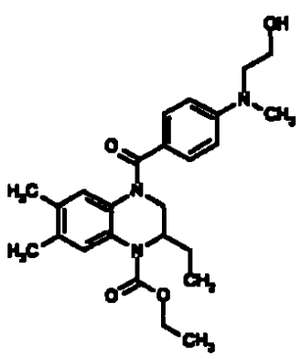
Ejemplo 233



Éster etílico del ácido 2-etil-4-(5-isobutil-isoxazol-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 414 (MH+).

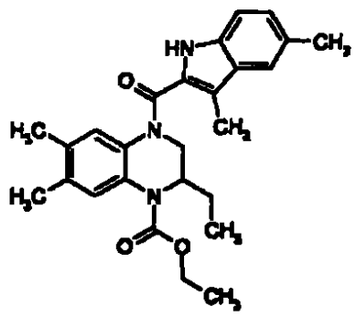
Ejemplo 234



Éster etílico del ácido 2-etil-4-{4-[(2-hidroxi-etil)-metil-amino]-benzoil}-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 440 (MH+).

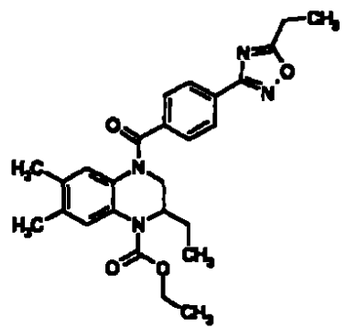
Ejemplo 235



Éster etílico del ácido 4-(3,5-dimetil-1*H*-indol-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 434 (MH+).

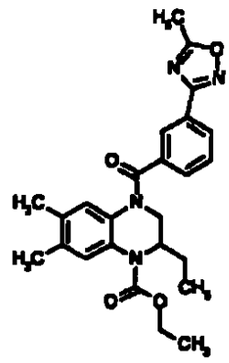
Ejemplo 236



Éster etílico del ácido 2-etil-4-[4-(5-etil-[1,2,4]-oxadiazol-3-il)-benzoil]-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 463 (MH+).

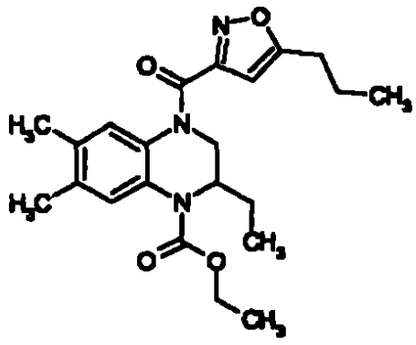
Ejemplo 237



Éster etílico del ácido 2-etil-6,7-dimetil-4-[3-(5-metil-[1,2,4]-oxadiazol-3-il)-benzoil]-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 449 (MH+).

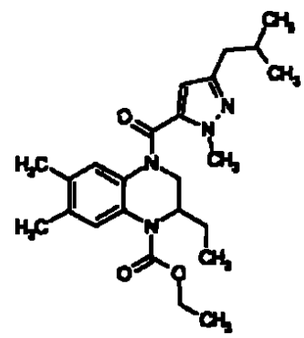
Ejemplo 238



Éster etílico del ácido 2-etil-6,7-dimetil-4-(5-propil-isoxazol-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 400 (MH+).

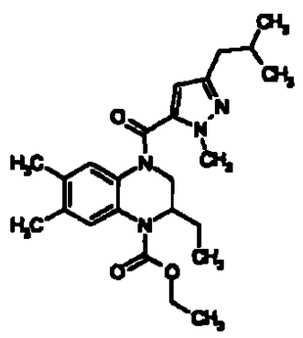
Ejemplo 239



Éster etílico del ácido 2-etil-4-(5-isobutil-2-metil-2*H*-pirazol-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

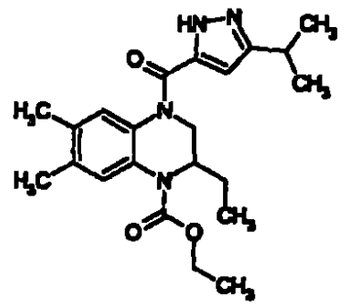
Ejemplo 240



Éster etílico del ácido 2-etil-4-(5-metoximetil-furan-2-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 401 (MH+).

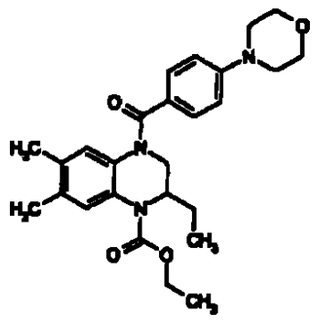
Ejemplo 241



Éster etílico del ácido 2-etil-4-(5-isopropil-2*H*-pirazol-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 399 (MH+).

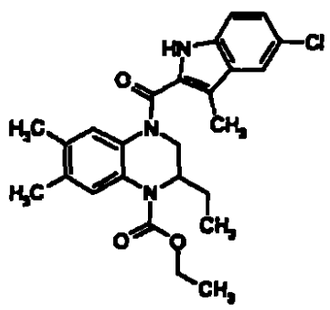
Ejemplo 242



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-morfolin-4-il-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 452 (MH+).

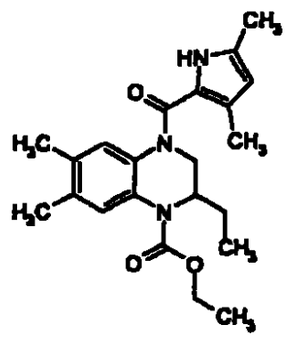
Ejemplo 243



Éster etílico del ácido 4-(5-cloro-3-metil-1*H*-indol-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 454 (MH+).

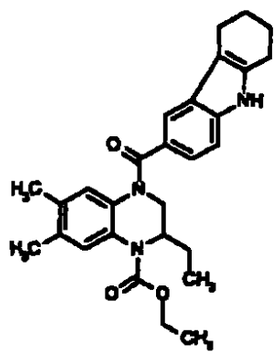
Ejemplo 244



Éster etílico del ácido 4-(3,5-dimetil-1*H*-pirrol-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 384 (MH+).

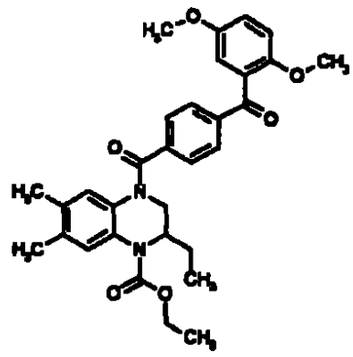
Ejemplo 245



Éster etílico del ácido 2-etil-6,7-dimetil-4-(6,7,8,9-tetrahidro-5*H*-carbazol-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 460 (MH+).

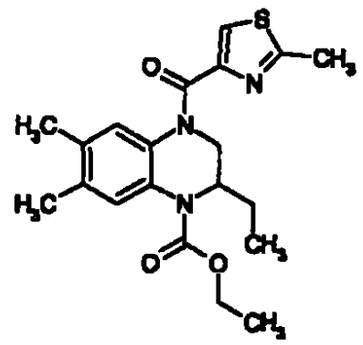
Ejemplo 246



Éster etílico del ácido 4-[4-(2,5-dimetoxi-benzoil)-benzoil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 531 (MH+).

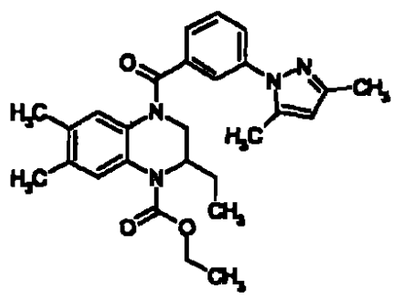
Ejemplo 247



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-metil-tiazol-4-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 388 (MH+).

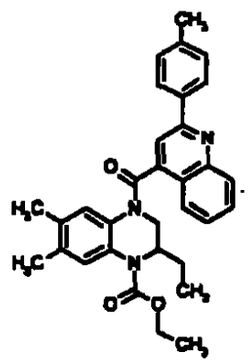
Ejemplo 248



Éster etílico del ácido 4-[3-(3,5-dimetil-pirazol-1-il)-benzoil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

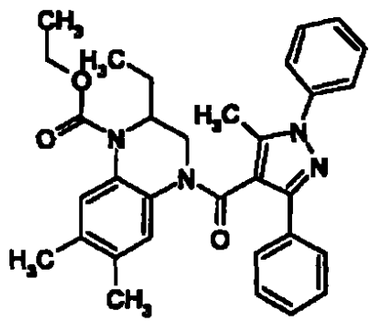
Ejemplo 249



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-p-tolil-quinolin-4-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 508 (MH+).

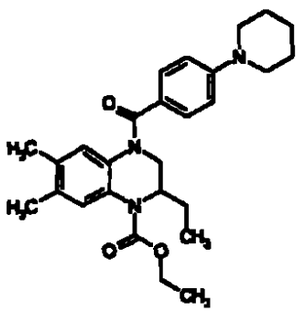
Ejemplo 250



Éster etílico del ácido 2-etil-6,7-dimetil-4-(5-metil-1,3-difenil-1*H*-pirazol-4-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 523 (MH+).

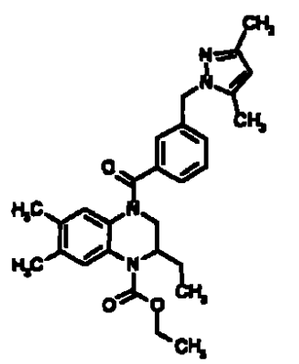
Ejemplo 251



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-piperidin-1-il-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 450 (MH+).

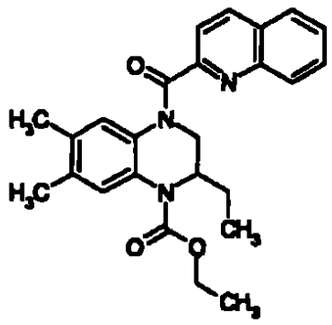
Ejemplo 252



Éster etílico del ácido 4-[3-(3,5-dimetil-pirazol-1-ilmetil)-benzoil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 475 (MH+).

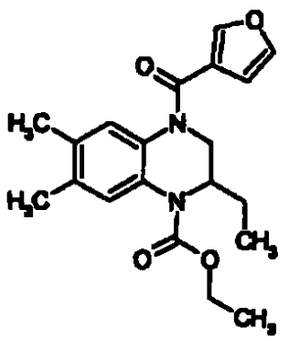
Ejemplo 253



Éster etílico del ácido 2-etil-6,7-dimetil-4-(quinolin-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 418 (MH+).

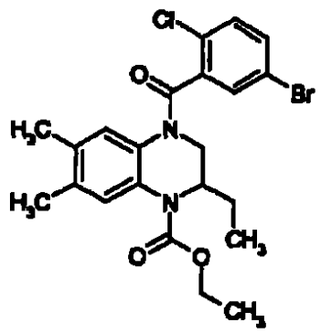
Ejemplo 254



Éster etílico del ácido 2-etil-4-(furan-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 357 (MH+).

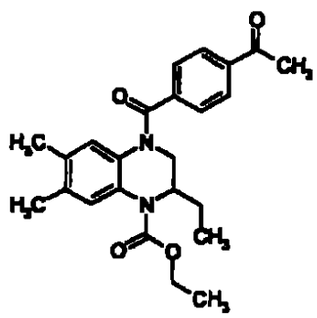
Ejemplo 255



Éster etílico del ácido 4-(5-bromo-2-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 480 (MH+).

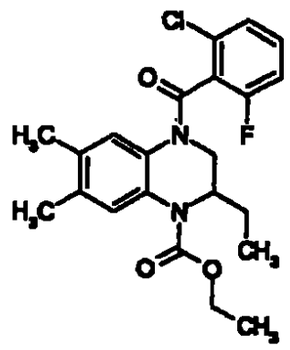
Ejemplo 256



Éster etílico del ácido 4-(4-acetil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 409 (MH+).

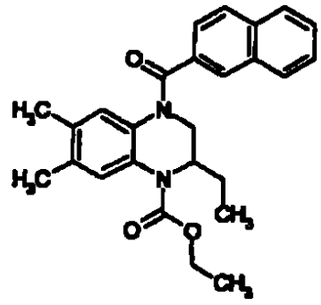
Ejemplo 257



Éster etílico del ácido 4-(2-cloro-6-fluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 419 (MH+).

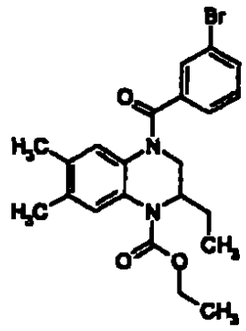
Ejemplo 258



Éster etílico del ácido 2-etil-6,7-dimetil-4-(naftalen-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 417 (MH+).

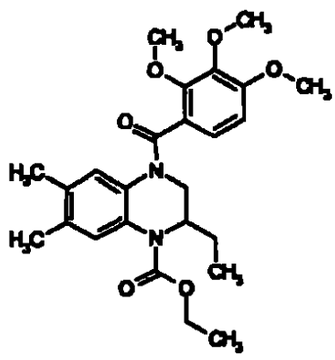
Ejemplo 259



Éster etílico del ácido 4-(3-bromo-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 446 (MH+).

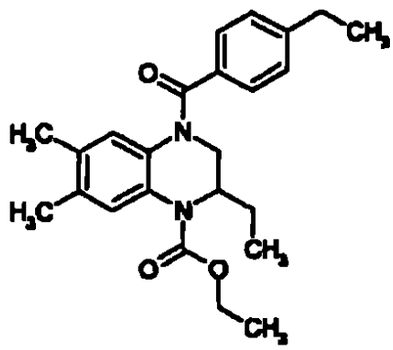
Ejemplo 260



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2,3,4-trimetoxi-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 457 (MH+).

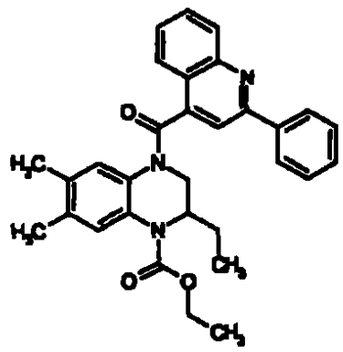
Ejemplo 261



Éster etílico del ácido 2-etil-4-(4-etil-benzoil)-6,7-dimetil--3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 395 (MH+).

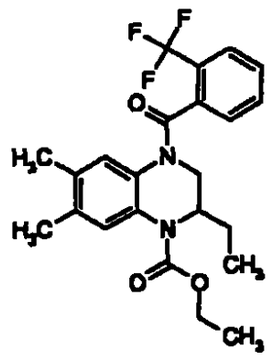
Ejemplo 262



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-fenil-quinolin-4-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 494 (MH+).

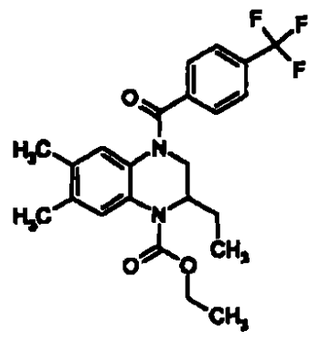
Ejemplo 263



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-trifluorometil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 435 (MH+).

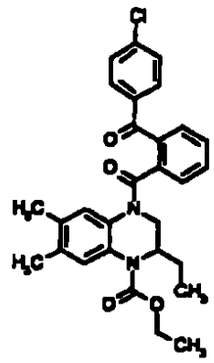
Ejemplo 264



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-trifluorometil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 435 (MH+).

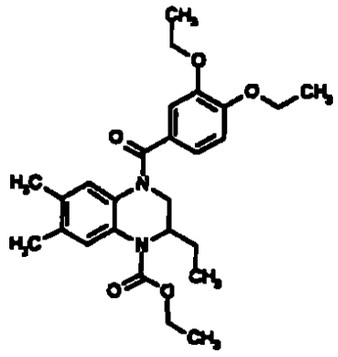
Ejemplo 265



Éster etílico del ácido 4-[2-(4-cloro-benzoil)-benzoil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 506 (MH+).

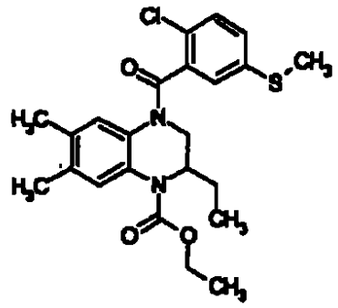
Ejemplo 266



Éster etílico del ácido 4-(3,4-dietoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 455 (MH+).

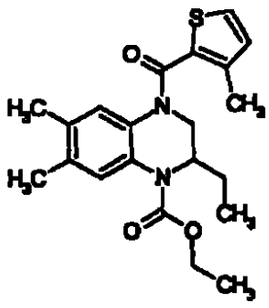
Ejemplo 267



Éster etílico del ácido 4-(2-cloro-5-metilsulfanil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 448 (MH+).

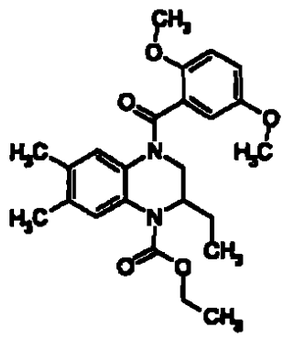
Ejemplo 268



Éster etílico del ácido 2-etil-6,7-dimetil-4-(3-metil-tiofeno-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 387 (MH+).

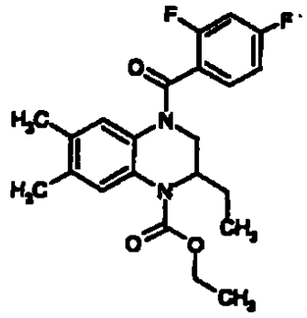
Ejemplo 269



Éster etílico del ácido 4-(2,5-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

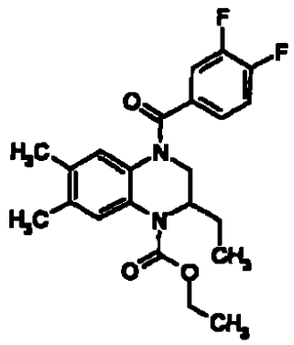
Ejemplo 270



Éster etílico del ácido 4-(2,4-difluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 403 (MH+).

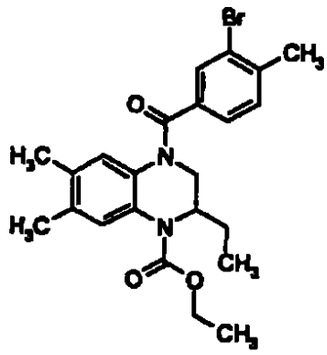
Ejemplo 271



Éster etílico del ácido 4-(3,4-difluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 403 (MH+).

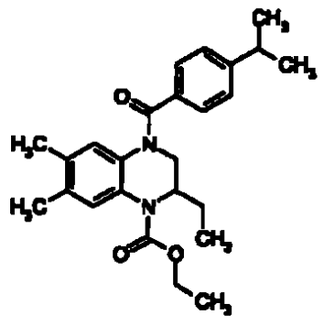
Ejemplo 272



Éster etílico del ácido 4-(3-bromo-4-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 460 (MH+).

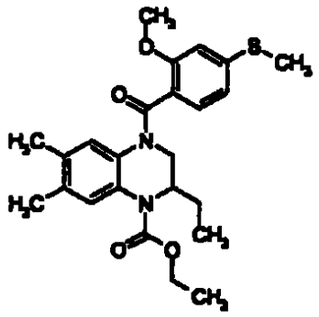
Ejemplo 273



Éster etílico del ácido 2-etil-4-(4-isopropil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 409 (MH+).

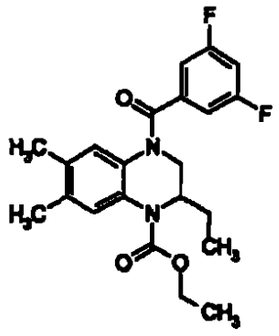
Ejemplo 274



Éster etílico del ácido 2-etil-4-(2-metoxi-4-metilsulfanil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 443 (MH+).

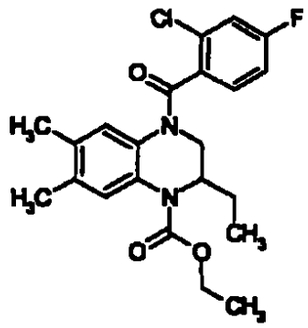
Ejemplo 275



Éster etílico del ácido 4-(3,5-difluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 403 (MH+).

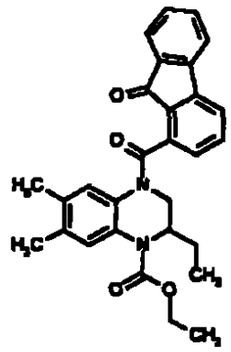
Ejemplo 276



Éster etílico del ácido 4-(2-cloro-4-fluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 419 (MH+).

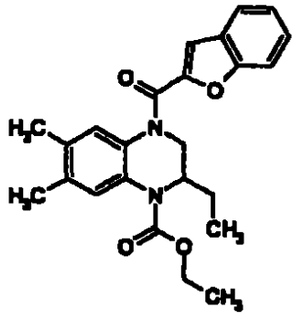
Ejemplo 277



Éster etílico del ácido 2-etil-6,7-dimetil-4-(9-oxo-9*H*-fluoren-1-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 469 (MH+).

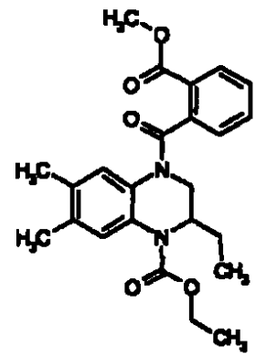
Ejemplo 278



Éster etílico del ácido 4-(benzofuran-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 407 (MH+).

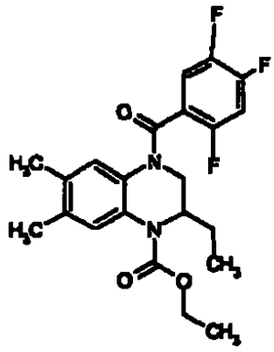
Ejemplo 279



Éster etílico del ácido 2-etil-4-(2-metoxicarbonil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 425 (MH+).

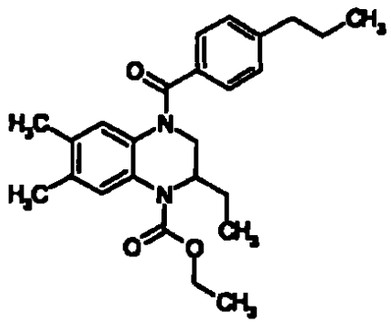
Ejemplo 280



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2,4,5-trifluoro-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 421 (MH+).

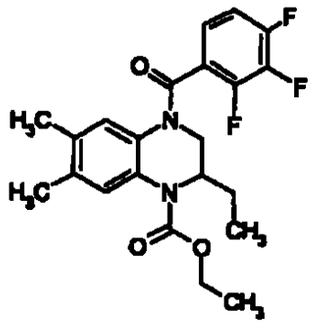
Ejemplo 281



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-propil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 409 (MH+).

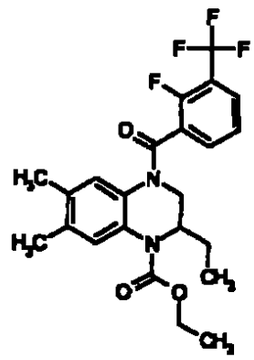
Ejemplo 282



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2,3,4-trifluoro-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 421 (MH+).

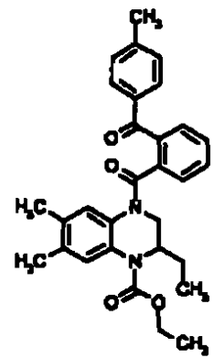
Ejemplo 283



Éster etílico del ácido 2-etil-4-(2-fluoro-3-trifluorometil-benzoil)-6,7-dimetil- 3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 453 (MH+).

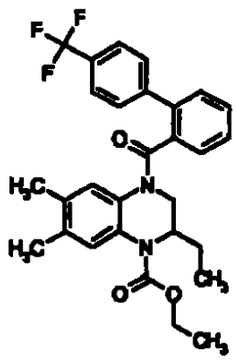
Ejemplo 284



Éster etílico del ácido 2-etil-6,7-dimetil-4-[2-(4-metil-benzoil)-benzoil]-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 485 (MH+).

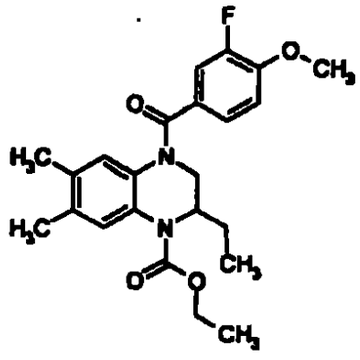
Ejemplo 285



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4'-trifluorometil-bifenil-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 511 (MH+).

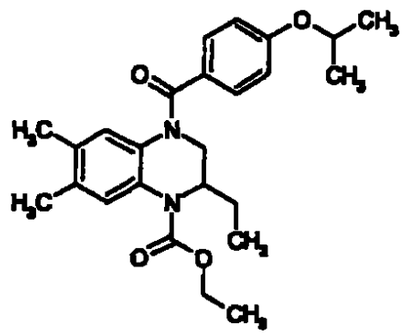
Ejemplo 286



Éster etílico del ácido 2-etil-4-(3-fluoro-4-metoxi-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 415 (MH+).

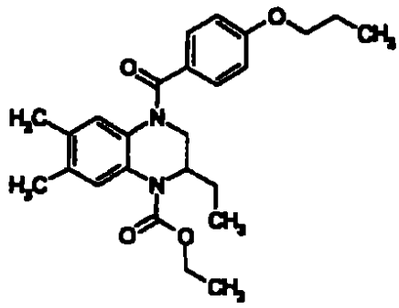
Ejemplo 287



Éster etílico del ácido 2-etil-4-(4-isopropoxi-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 425 (MH+).

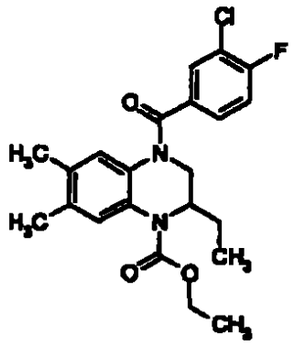
Ejemplo 288



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-propoxi-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 425 (MH+).

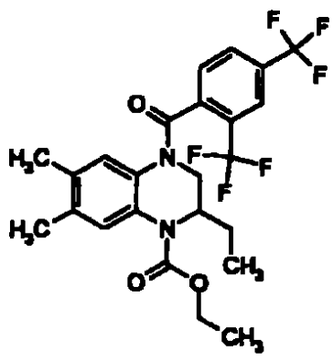
Ejemplo 289



Éster etílico del ácido 4-(3-cloro-4-fluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 419 (MH+).

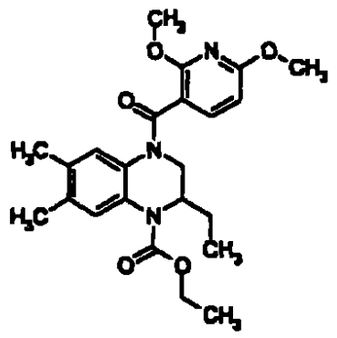
Ejemplo 290



Éster etílico del ácido 4-(2,4-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 503 (MH+).

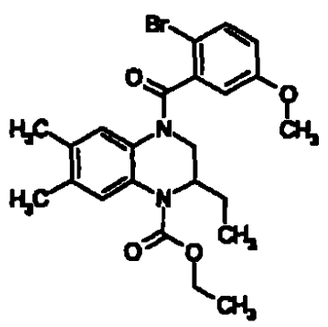
Ejemplo 291



Éster etílico del ácido 4-(2,6-dimetoxi-piridin-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 428 (MH+).

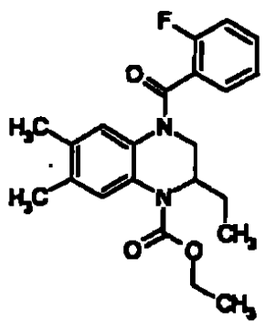
Ejemplo 292



Éster etílico del ácido 4-(2-bromo-5-metoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 476 (MH+).

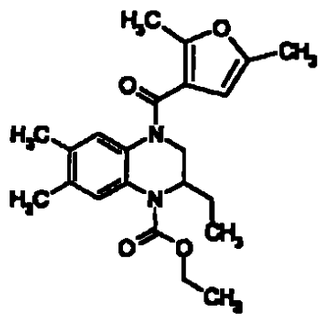
Ejemplo 293



Éster etílico del ácido 2-etil-4-(2-fluoro-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 385 (MH+).

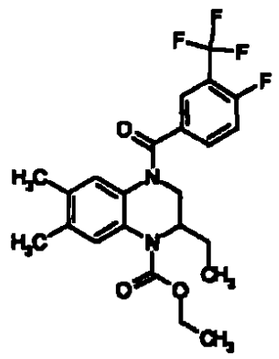
Ejemplo 294



Éster etílico del ácido 4-(2,5-D-metil-furan-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 385 (MH+).

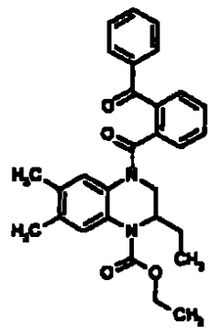
Ejemplo 295



Éster etílico del ácido 2-etil-4-(4-fluoro-3-trifluorometil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 453 (MH+).

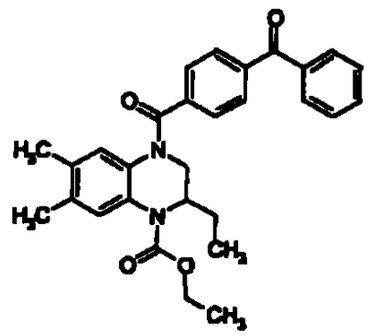
Ejemplo 296



Éster etílico del ácido 4-(2-benzoil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 471 (MH+).

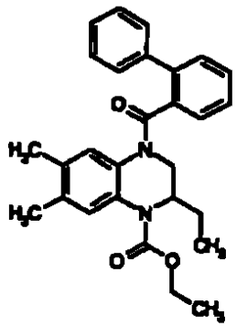
Ejemplo 297



Éster etílico del ácido 4-(4-benzoil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 471 (MH+).

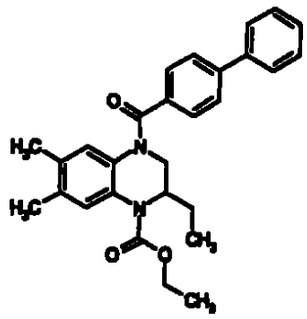
Ejemplo 298



Éster etílico del ácido 4-(bifenil-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 443 (MH+).

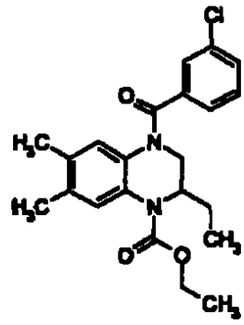
Ejemplo 299



Éster etílico del ácido 4-(bifenil-4-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 443 (MH+).

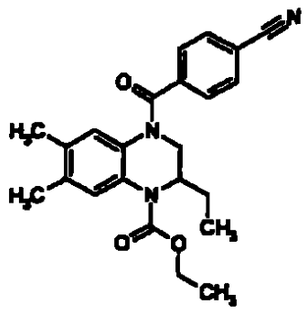
Ejemplo 300



Éster etílico del ácido 4-(3-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 401 (MH+).

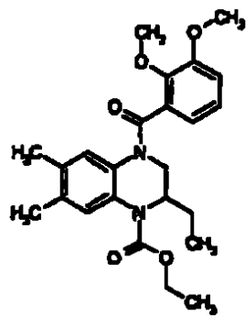
Ejemplo 301



Éster etílico del ácido 4-(4-ciano-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 392 (MH+).

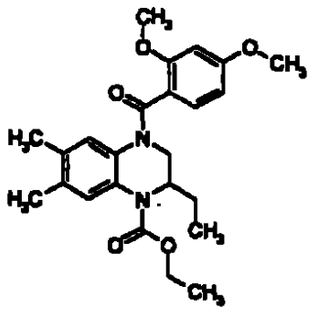
Ejemplo 302



Éster etílico del ácido 4-(2,3-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

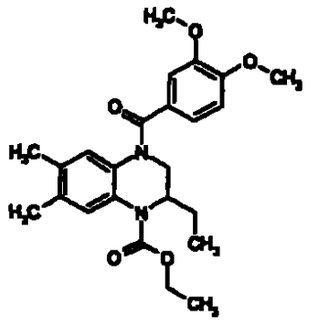
Ejemplo 303



Éster etílico del ácido 4-(2,4-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

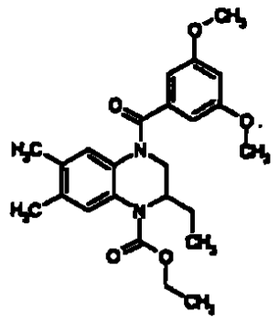
Ejemplo 304



Éster etílico del ácido 4-(3,4-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

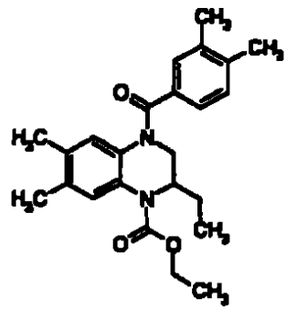
Ejemplo 305



Éster etílico del ácido 4-(3,5-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

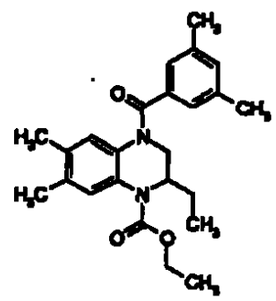
Ejemplo 306



Éster etílico del ácido 4-(3,4-dimetil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 395 (MH+).

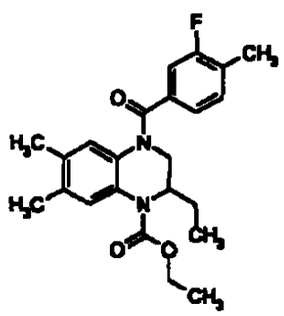
Ejemplo 307



Éster etílico del ácido 4-(3,5-dimetil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 395 (MH+).

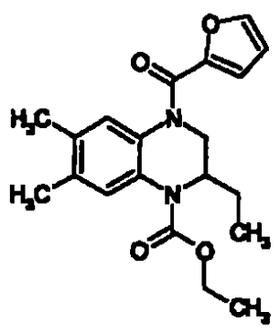
Ejemplo 308



Éster etílico del ácido 2-etil-4-(3-fluoro-4-metil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 399 (MH+).

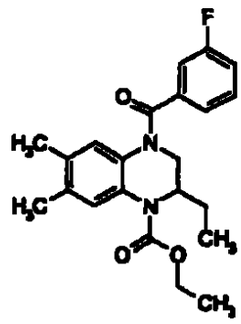
Ejemplo 309



Éster etílico del ácido 2-etil-4-(furan-2-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 357 (MH+).

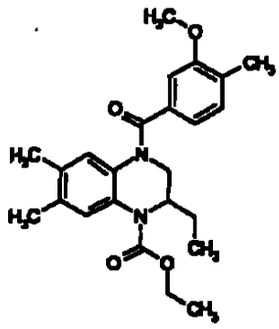
Ejemplo 310



Éster etílico del ácido 2-etil-4-(3-fluoro-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 385 (MH+).

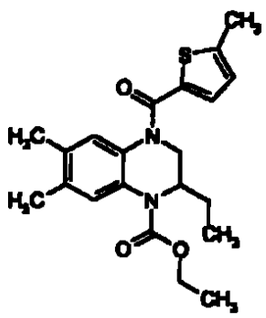
Ejemplo 311



Éster etílico del ácido 2-etil-4-(3-metoxi-4-metil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 411 (MH+).

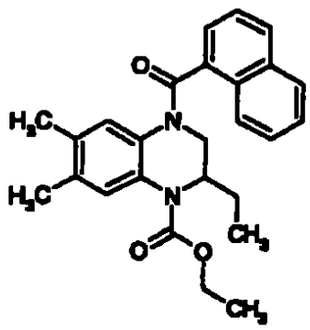
Ejemplo 312



Éster etílico del ácido 2-etil-6,7-dimetil-4-(5-metil-tiofeno-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 387 (MH+).

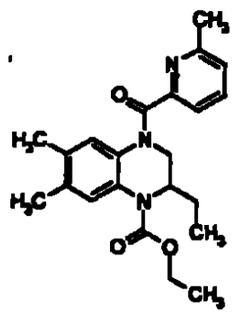
Ejemplo 313



Éster etílico del ácido 2-etil-6,7-dimetil-4-(naftalen-1-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 417 (MH+).

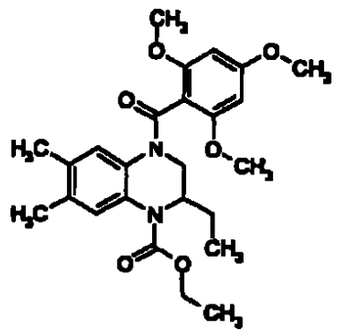
Ejemplo 314



Éster etílico del ácido 2-etil-6,7-dimetil-4-(6-metil-piridin-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 382 (MH+).

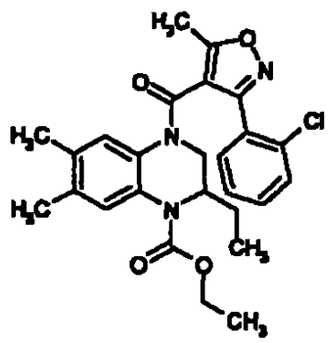
Ejemplo 315



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2,4,6-trimetoxi-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 457 (MH+).

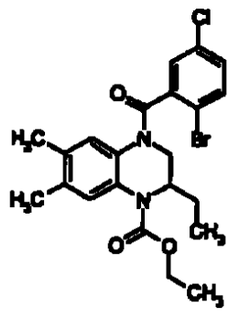
Ejemplo 316



Éster etílico del ácido 4-[3-(2-cloro-fenil)-5-metil-isoxazol-4-carbonil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 482 (MH+).

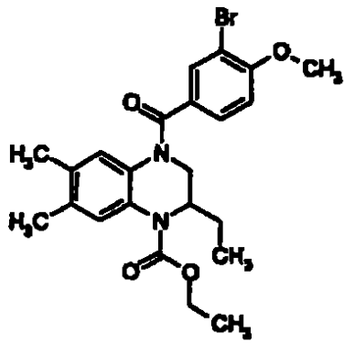
Ejemplo 317



Éster etílico del ácido 4-(2-bromo-5-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 480 (MH+).

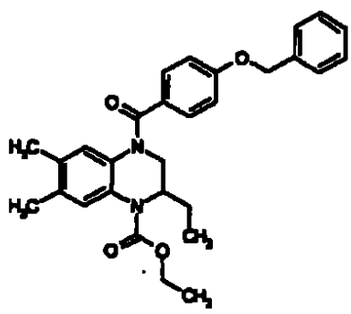
Ejemplo 318



Éster etílico del ácido 4-(3-bromo-4-metoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 476 (MH+).

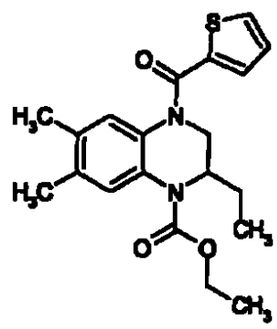
Ejemplo 319



Éster etílico del ácido 4-(4-benciloxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 473 (MH+).

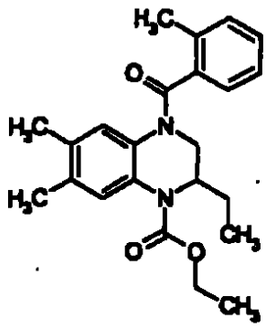
Ejemplo 320



Éster etílico del ácido 2-etil-6,7-dimetil-4-(tiofen-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 373 (MH+).

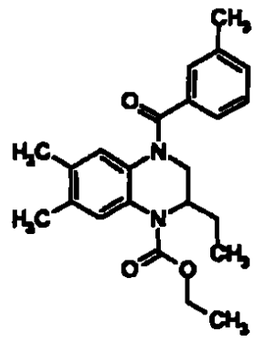
Ejemplo 321



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-metil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 381 (MH+).

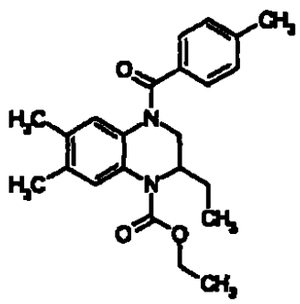
Ejemplo 322



Éster etílico del ácido 2-etil-6,7-dimetil-4-(3-metil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 381 (MH+).

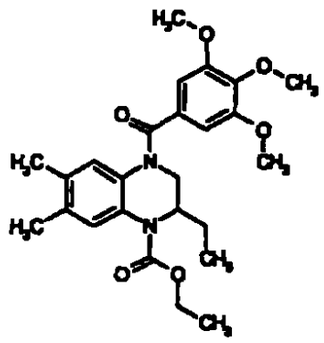
Ejemplo 323



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-metil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): (MH+).

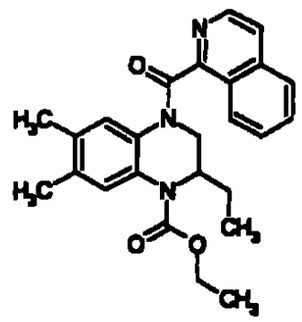
Ejemplo 324



Éster etílico del ácido 2-etil-6,7-dimetil-4-(3,4,5-trimetoxi-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 457 (MH+).

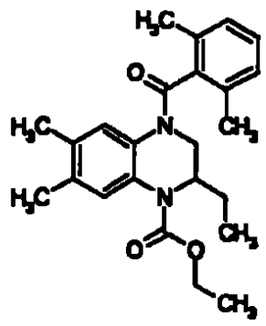
Ejemplo 325



Éster etílico del ácido 2-etil-4-(isoquinolin-1-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 418 (MH+).

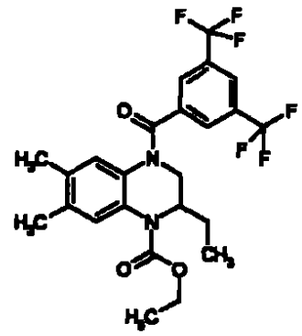
Ejemplo 326



Éster etílico del ácido 4-(2,6-dimetil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 395 (MH+).

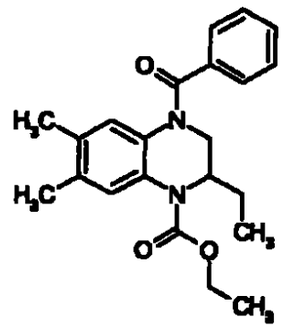
Ejemplo 327



Éster etílico del ácido 4-(3,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 503 (MH+).

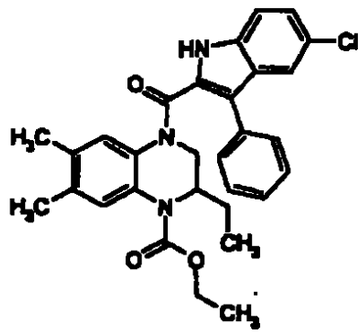
Ejemplo 328



Éster etílico del ácido 4-benzoil-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 367 (MH+).

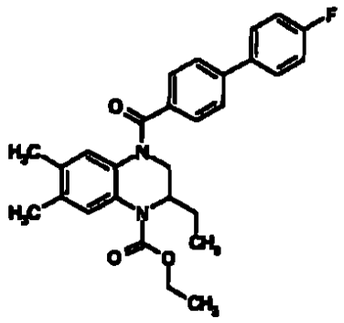
Ejemplo 329



Éster etílico del ácido 4-(5-cloro-3-fenil-1*H*-indol-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 517 (MH+).

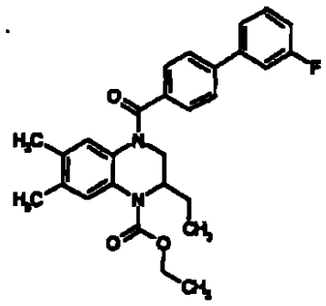
Ejemplo 330



Éster etílico del ácido 2-etil-4-(4'-fluoro-bifenil-4-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

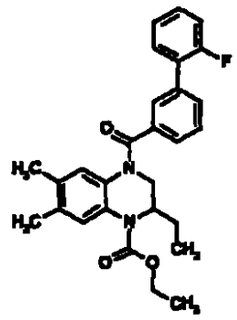
Ejemplo 331



Éster etílico del ácido 2-etil-4-(3'-fluoro-bifenil-4-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

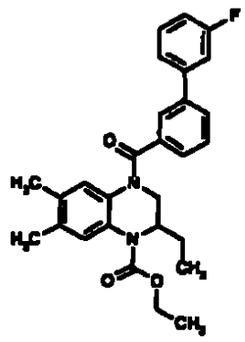
Ejemplo 332



Éster etílico del ácido 2-etil-4-(2'-fluoro-bifenil-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

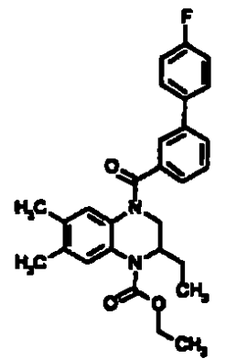
Ejemplo 333



Éster etílico del ácido 2-etil-4-(3'-fluoro-bifenil-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

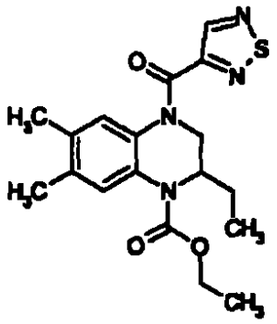
Ejemplo 334



Éster etílico del ácido 2-etil-4-(4'-fluoro-bifenil-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

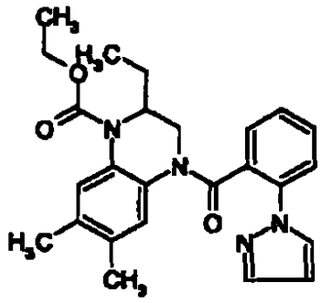
Ejemplo 335



Éster etílico del ácido 2-etil-6,7-dimetil-4-([1,2,5]tiadiazol-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 375 (MH+).

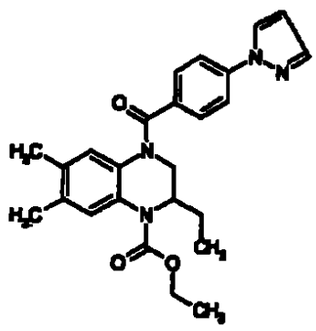
Ejemplo 336



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-pirazol-1-il-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 433 (MH+).

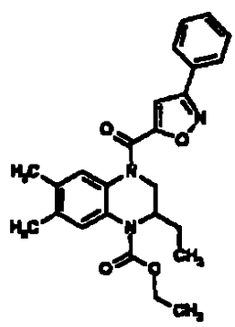
Ejemplo 337



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-pirazol-1-il-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 433 (MH+).

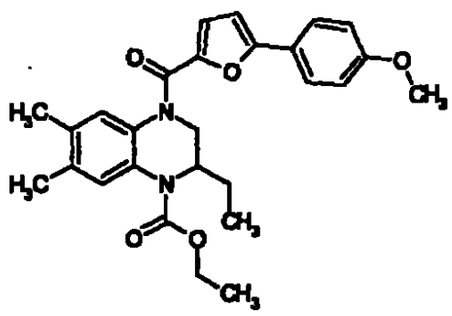
Ejemplo 338



Éster etílico del ácido 2-etil-6,7-dimetil-4-(3-fenil-isoxazol-5-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 434 (MH+).

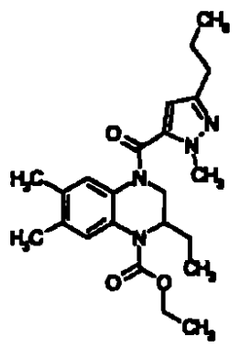
Ejemplo 339



Éster etílico del ácido 2-etil-4-[5-(4-metoxi-fenil)-furan-2-carbonil]-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 463 (MH+).

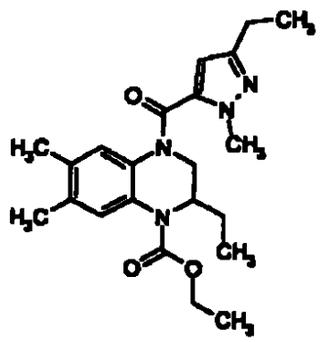
Ejemplo 340



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-metil-5-propil-2*H*-pirazol-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 413 (MH+).

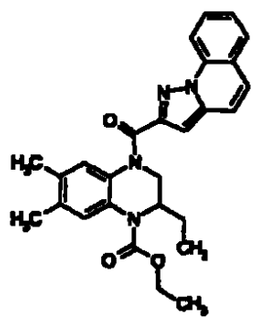
Ejemplo 341



Éster etílico del ácido 2-etil-4-(5-etil-2-metil-2*H*-pirazol-3-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 399 (MH+).

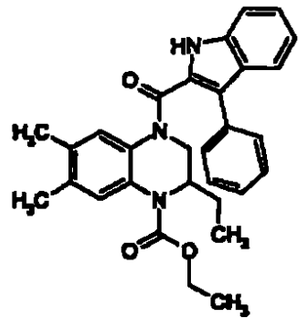
Ejemplo 342



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-pirazolo[1,5-a]alquinolin-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 457 (MH+).

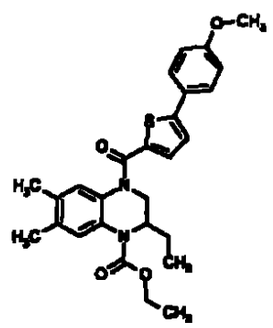
Ejemplo 343



Éster etílico del ácido 2-etil-6,7-dimetil-4-(3-fenil-1*H*-indol-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 482 (MH+).

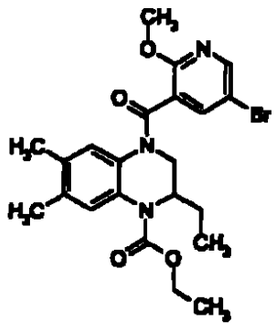
Ejemplo 344



Éster etílico del ácido 2-etil-4-[5-(4-metoxi-fenil)-tiofen-2-carbonil]-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 479 (MH+).

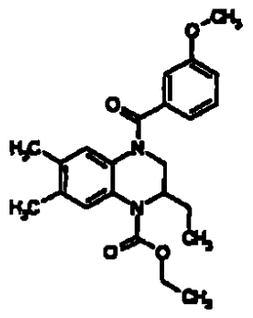
Ejemplo 345



Éster etílico del ácido 4-(5-bromo-2-metoxi-piridin-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 477 (MH+).

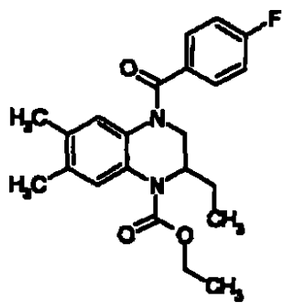
Ejemplo 346



Éster etílico del ácido 2-etil-4-(3-metoxi-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 397 (MH+).

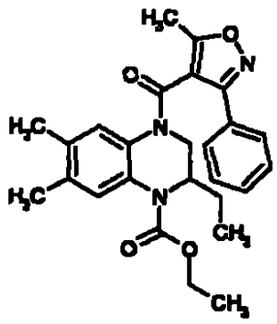
Ejemplo 347



Éster etílico del ácido 2-etil-4-(4-fluoro-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 385 (MH+).

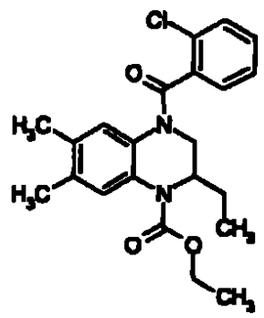
Ejemplo 348



Éster etílico del ácido 2-etil-6,7-dimetil-4-(5-metil-3-fenil-isoxazol-4-carbonil)- 3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 448 (MH+).

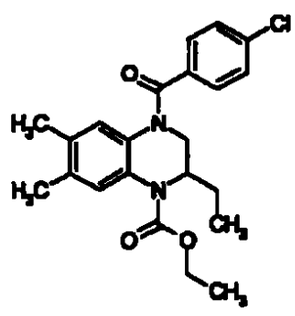
Ejemplo 349



Éster etílico del ácido 4-(2-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 401 (MH+).

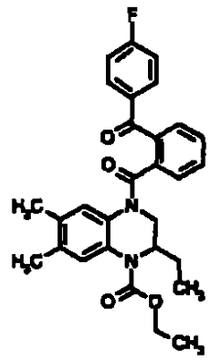
Ejemplo 350



Éster etílico del ácido 4-(4-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 401 (MH+).

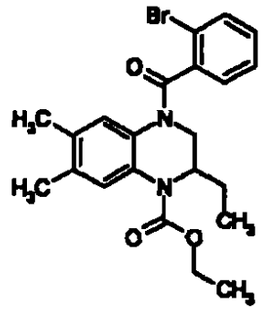
Ejemplo 351



Éster etílico del ácido 2-etil-4-(4-fluoro-benzoil]-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 489 (MH+).

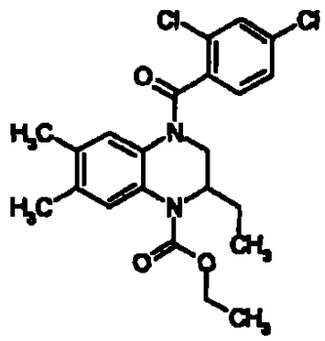
Ejemplo 352



Éster etílico del ácido 4-(2-bromo-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 446 (MH+).

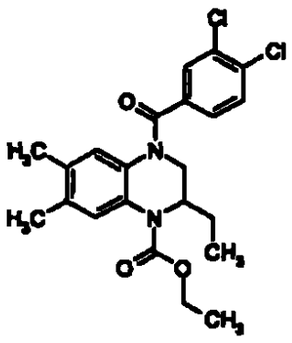
Ejemplo 353



Éster etílico del ácido 4-(2,4-dicloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 436 (MH+).

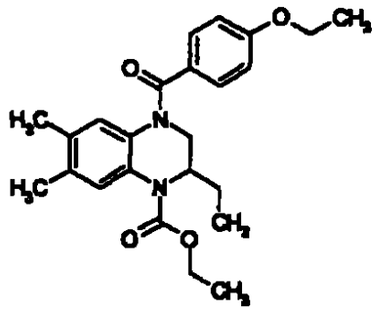
Ejemplo 354



Éster etílico del ácido 4-(3,4-dicloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 436 (MH+).

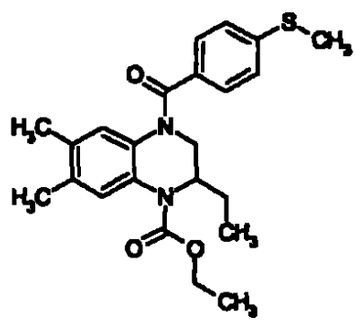
Ejemplo 355



Éster etílico del ácido 4-(4-etoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 411 (MH+).

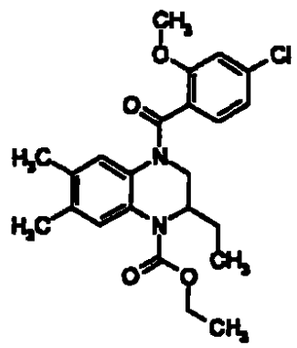
Ejemplo 356



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-metilsulfanil-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 413 (MH+).

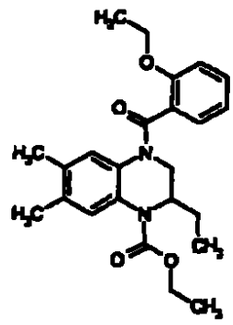
Ejemplo 357



Éster etílico del ácido 4-(4-cloro-2-metoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 431 (MH+).

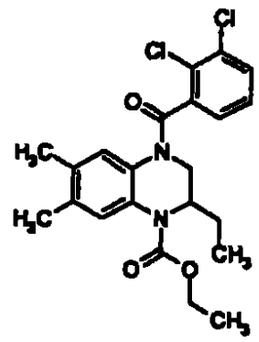
Ejemplo 358



Éster etílico del ácido 4-(2-etoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 411 (MH+).

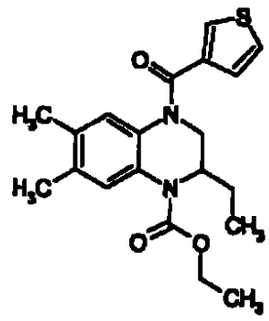
Ejemplo 359



Éster etílico del ácido 4-(2,3-dicloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 436 (MH+).

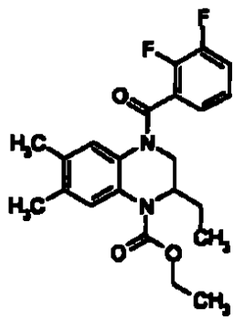
Ejemplo 360



Éster etílico del ácido 2-etil-6,7-dimetil-4-(tiofen-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 373 (MH+).

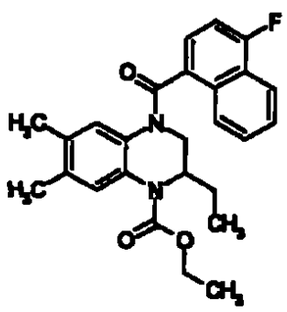
Ejemplo 361



Éster etílico del ácido 4-(2,3-difluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 403 (MH+).

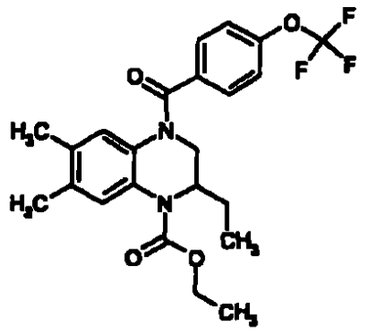
Ejemplo 362



Éster etílico del ácido 2-etil-4-(4-fluoro-naftalen-1-carbonil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 435 (MH+).

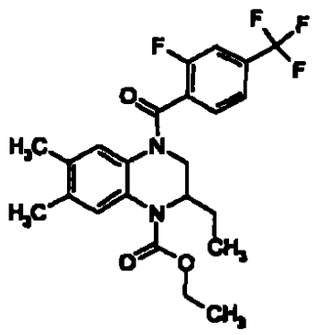
Ejemplo 363



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-trifluorometoxi-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 451 (MH+).

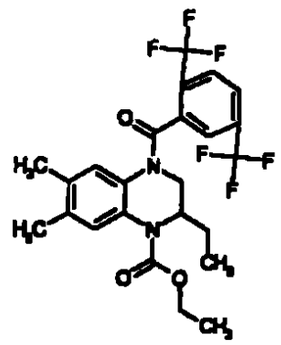
Ejemplo 364



Éster etílico del ácido 2-etil-4-(2-fluoro-trifluorometil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 453 (MH+).

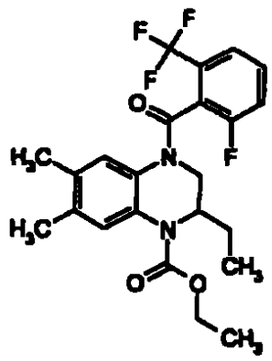
Ejemplo 365



Éster etílico del ácido 4-(2,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 503 (MH+).

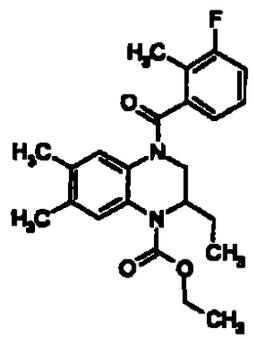
Ejemplo 366



Éster etílico del ácido 2-etil-4-(2-fluoro-6-trifluorometil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 453 (MH+).

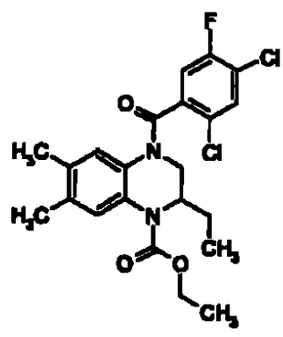
Ejemplo 367



Éster etílico del ácido 2-etil-4-(3-fluoro-2-metil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 399 (MH+).

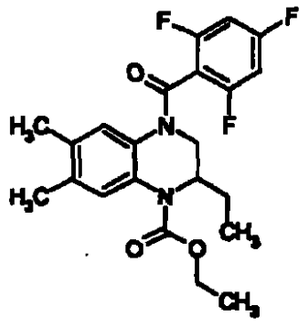
Ejemplo 368



Éster etílico del ácido 4-(2,4-dicloro-5-fluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 454 (MH+).

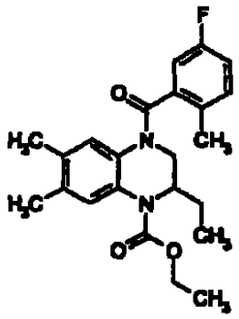
Ejemplo 369



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2,4,6-trifluoro-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 421 (MH+).

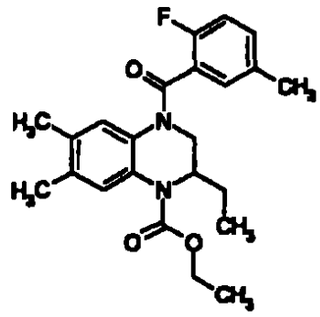
Ejemplo 370



Éster etílico del ácido 2-etil-4-(5-fluoro-2-metil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 399 (MH+).

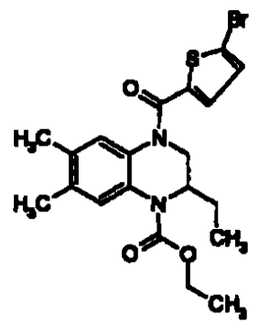
Ejemplo 371



Éster etílico del ácido 2-etil-4-(2-fluoro-5-metil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 399 (MH+).

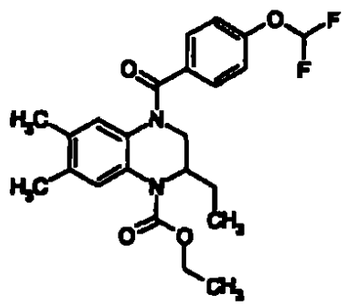
Ejemplo 372



Éster etílico del ácido 4-(5-bromo-tiofen-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 452 (MH+).

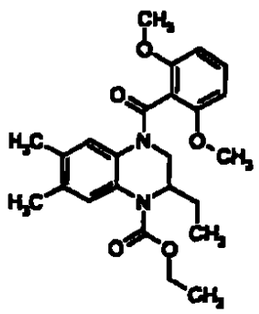
Ejemplo 373



Éster etílico del ácido 4-(4-difluorometoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 433 (MH+).

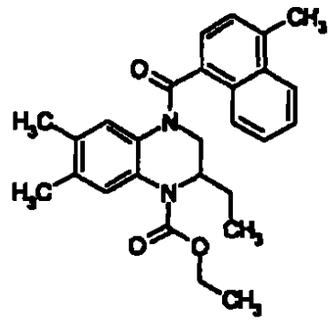
Ejemplo 374



Éster etílico del ácido 4-(2,6-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 427 (MH+).

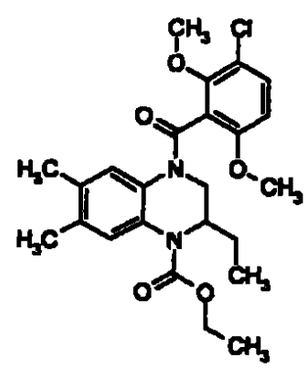
Ejemplo 375



Éster etílico del ácido 2-etil-6,7-dimetil-4-(4-metil-naftalen-1-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 431 (MH+).

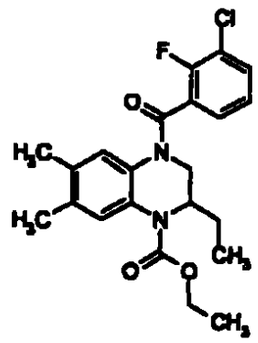
Ejemplo 376



Éster etílico del ácido 4-(3-cloro-2,6-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

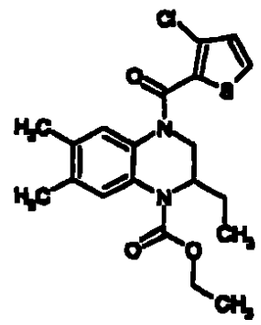
Ejemplo 377



Éster etílico del ácido 4-(3-cloro-2-fluoro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 419 (MH+).

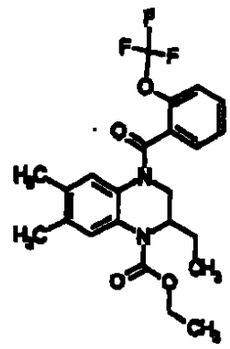
Ejemplo 378



Éster etílico del ácido 4-(3-cloro-tiofeno-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2H-quinoxalina-1-carboxílico

LC-MS (ESI+): 407 (MH+).

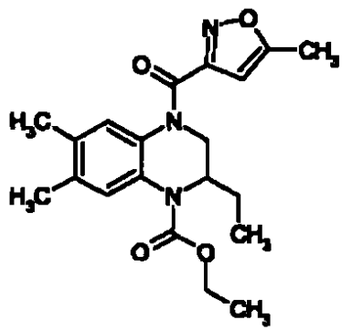
Ejemplo 379



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-trifluorometoxi-benzoil)-3,4-dihidro-2H-quinoxalina-1-carboxílico

LC-MS (ESI+): 451 (MH+).

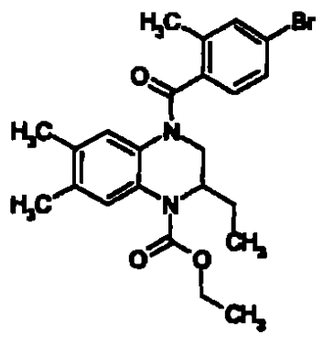
Ejemplo 380



Éster etílico del ácido 2-etil-6,7-dimetil-4-(5-metil-isoxazol-3-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 372 (MH+).

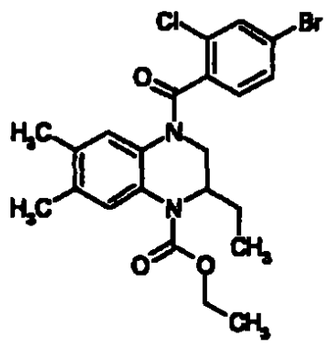
Ejemplo 381



Éster etílico del ácido 2-etil-6,7-dimetil-4-(3-metil-furan-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 371 (MH+).

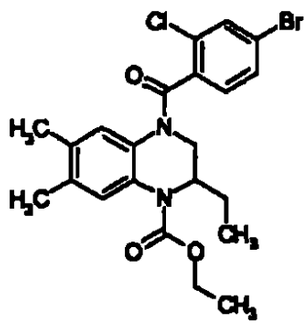
Ejemplo 382



Éster etílico del ácido 4-(4-bromo-2-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 460 (MH+).

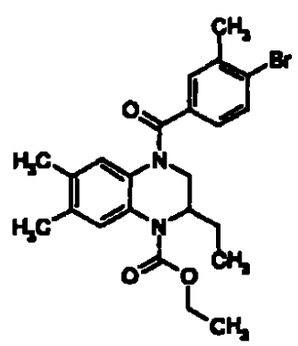
Ejemplo 383



Éster etílico del ácido 4-(4-bromo-2-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 480 (MH+).

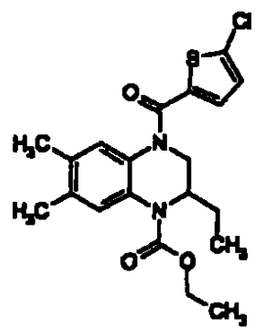
Ejemplo 384



Éster etílico del ácido 4-(4-bromo-3-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 460 (MH+).

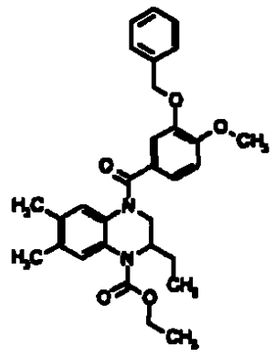
Ejemplo 385



Éster etílico del ácido 4-(5-cloro-tiofen-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 407 (MH+).

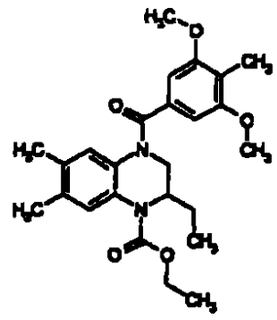
Ejemplo 386



Éster etílico del ácido 4-(3-benciloxi-4-metoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 503 (MH+).

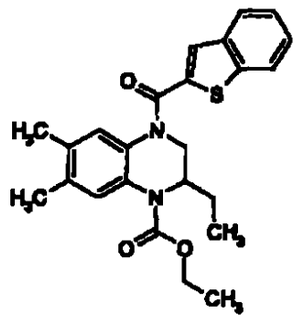
Ejemplo 387



Éster etílico del ácido 4-(3,5-dimetoxi-4-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 441 (MH+).

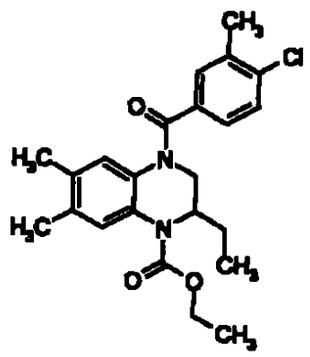
Ejemplo 388



Éster etílico del ácido 4-(benzo[b]tiofen-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 423 (MH+).

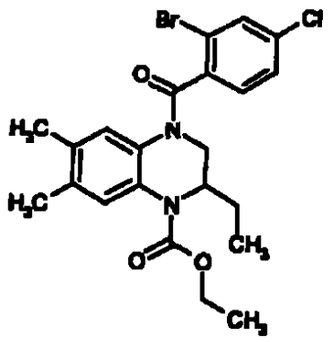
Ejemplo 389



Éster etílico del ácido 4-(4-cloro-3-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 415 (MH+).

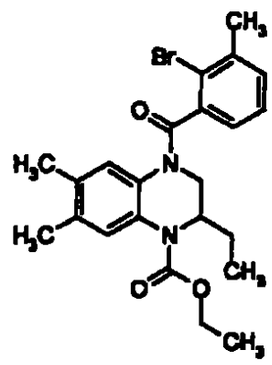
Ejemplo 390



Éster etílico del ácido 4-(2-bromo-4-cloro-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 480 (MH+).

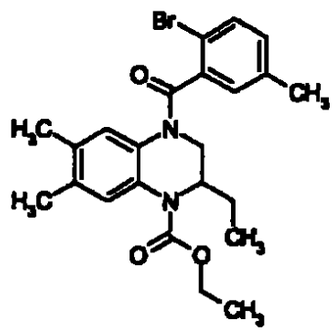
Ejemplo 391



Éster etílico del ácido 4-(2-bromo-3-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 460 (MH+).

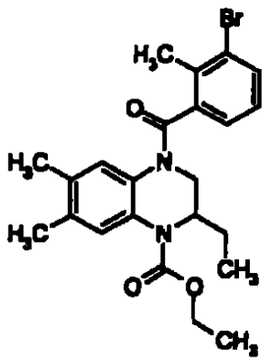
Ejemplo 392



Éster etílico del ácido 4-(2-bromo-5-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 460 (MH+).

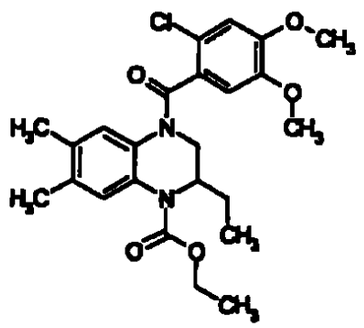
Ejemplo 393



Éster etílico del ácido 4-(3-bromo-2-metil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 460 (MH+).

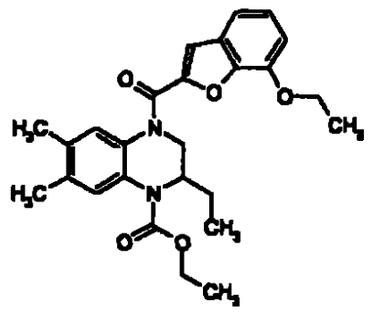
Ejemplo 394



Éster etílico del ácido 4-(2-cloro-4,5-dimetoxi-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 461 (MH+).

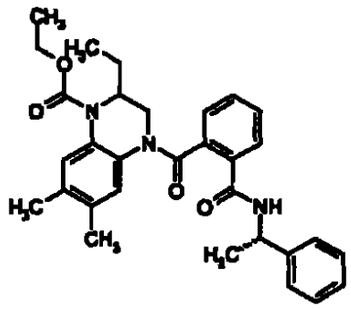
Ejemplo 395



Éster etílico del ácido 4-(7-etoxi-benzofuran-2-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 451 (MH+).

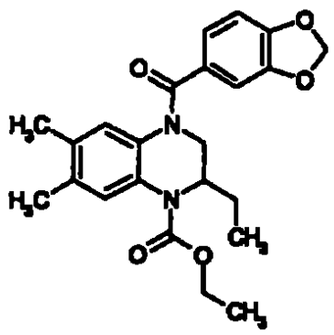
Ejemplo 396



Éster etílico del ácido 2-etil-6,7-dimetil-4-[2-(1-fenil-etilcarbamoil)-benzoil]-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 514 (MH+).

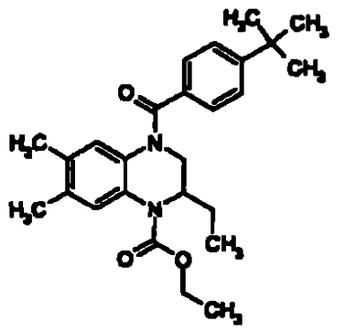
Ejemplo 397



Éster etílico del ácido 4-(benzo[1,3]dioxol-5-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 411 (MH+).

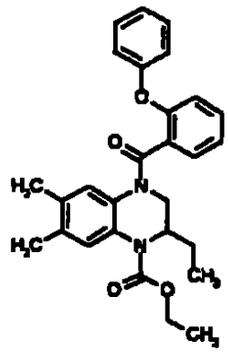
Ejemplo 398



Éster etílico del ácido 4-(4-terc-butil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 423 (MH+).

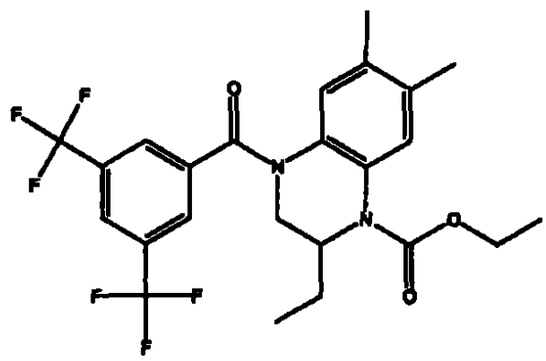
Ejemplo 399



Éster etílico del ácido 2-etil-6,7-dimetil-4-(2-fenoxi-benzoil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 459 (MH+).

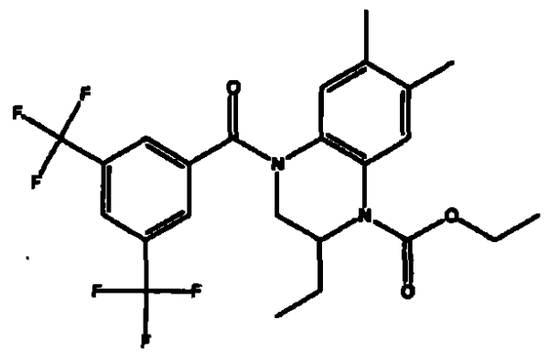
Ejemplo 400



Éster etílico del ácido 4-(3,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 503 (MH+).

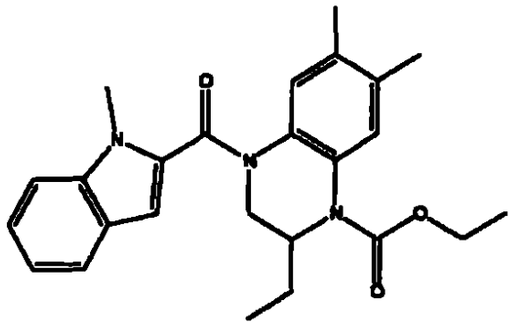
Ejemplo 401



Éster etílico del ácido 4-(3,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 503 (MH+).

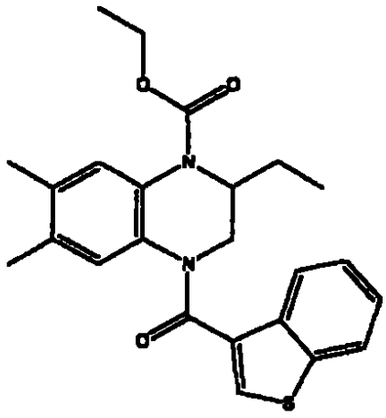
Ejemplo 402



Éster etílico del ácido 2-etil-6,7-dimetil-4-(1-metil-1*H*-indol-2-carbonil)-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 420 (MH+).

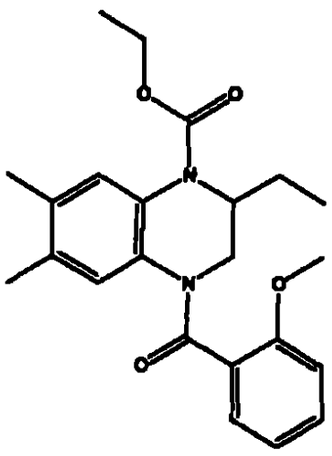
Ejemplo 403



Éster etílico del ácido 4-(benzo[b]tiofen-3-carbonil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 423 (MH+).

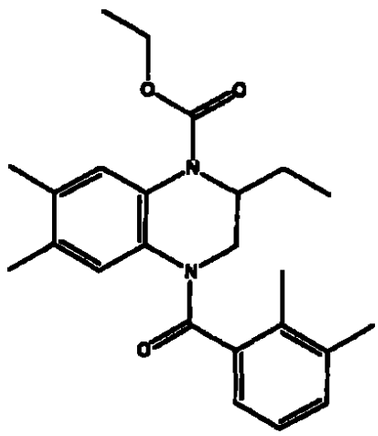
Ejemplo 404



Éster etílico del ácido 2-etil-4-(2-metoxi-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 397 (MH+).

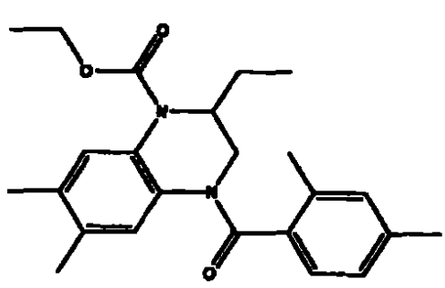
Ejemplo 405



Éster etílico del ácido 4-(2,3-dimetil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 395 (MH+).

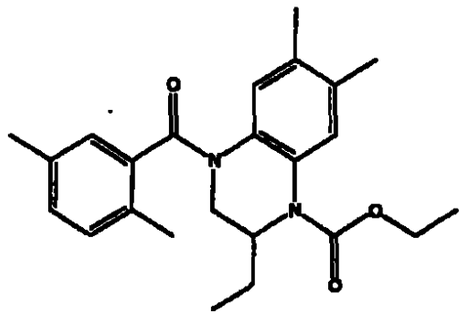
Ejemplo 406



Éster etílico del ácido 4-(2,4-dimetil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 395 (MH+).

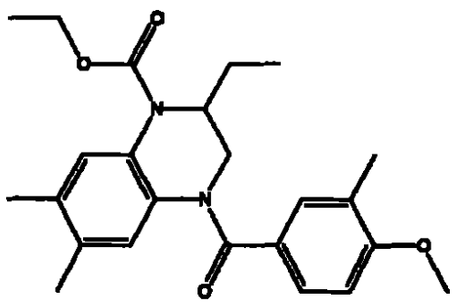
Ejemplo 407



Éster etílico del ácido 4-(2,5-dimetil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 395 (MH+).

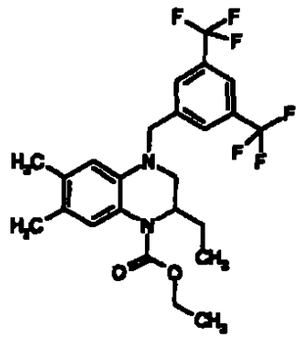
Ejemplo 408



Éster etílico del ácido 2-etil-4-(4-metoxi-3-metil-benzoil)-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

LC-MS (ESI+): 411 (MH+).

Ejemplo 409



Preparación del éster etílico del ácido 4-(3,5-bis-trifluorometil-bencil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

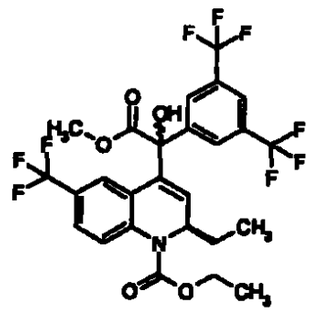
Una solución de éster etílico de ácido 2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico (0,05 g, 1 eq, 0,19 mmol), bromuro de 3,5-bis-(trifluorometil)bencilo (0,038 ml, 2,2 eq, 0,42 mmol) y trietilamina (0,062 ml, 3 eq, 0,57 mmol) en acetonitrilo (2 ml) se trató con yoduro de potasio catalítico y se sometió a dos ciclos de diez minutos en un microondas químico Emrys Optimizer (Personal Chemistry, Uppsala, Suecia) a 180°C. La reacción se evaporó a sequedad y se purificó en el sistema de HPLC preparativa de Shimadzu Corporation (Kyoto, Japón) usando un gradiente de 40-100% de acetonitrilo/agua de 6 minutos, tiempo total 8 minutos, para proporcionar el compuesto del título (0,0045 mg, 5%).

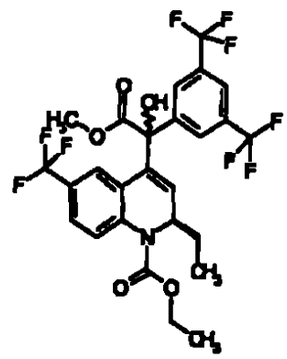
^{1}H RMN ($CDCl_3$): □ 0,90 (t, H = 7,47 Hz, 3H), 1,31 (t, J = 7,05 Hz, 3H), 1,46 (m, 2H), 2,11 (s, 3H), 2,16 (s, 3H), 3,17 (dd, J = 11,28, 1,24 Hz, 1H), 3,49 (dd, J = 11,16, 4,15 Hz, 1H), 4,19 (m, 1H), 4,28 (m, 1H), 4,46 (d, J = 17,43 Hz,), 4,52 (m, 1H), 4,66 (d, J = 17,01 Hz), 6,31 (s, 1H), 7,29 (s a, 1H), 7,71 (s, 2H), 7,78 (s, 1H).

LCMS (ESI+): 489 (MH+)

Los ejemplos proféticos 410-427 pueden prepararse en forma enriquecida ópticamente por resolución del racemato correspondiente indicado, o de un intermedio en su síntesis, usando procedimientos análogos a los descritos en este documento:

Ejemplo 410 (Estereoisómeros del Ejemplo 2)





Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

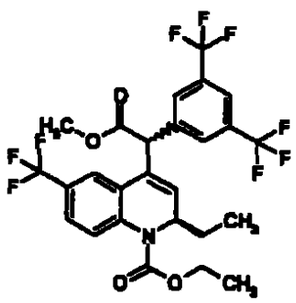
Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

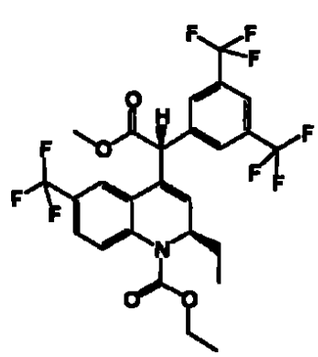
Éster etílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico; o

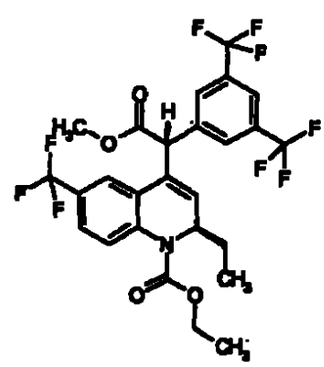
Éster etílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 411 (Estereoisómeros de los Ejemplo 3 y 4)



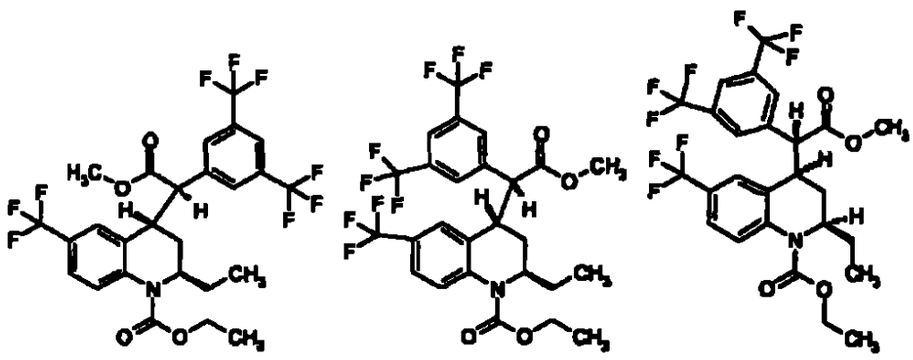




Éster etílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico; o

Éster etílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico; o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 412 (Estereoisómeros de los Ejemplo 5, 6, 7 y 8)



Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

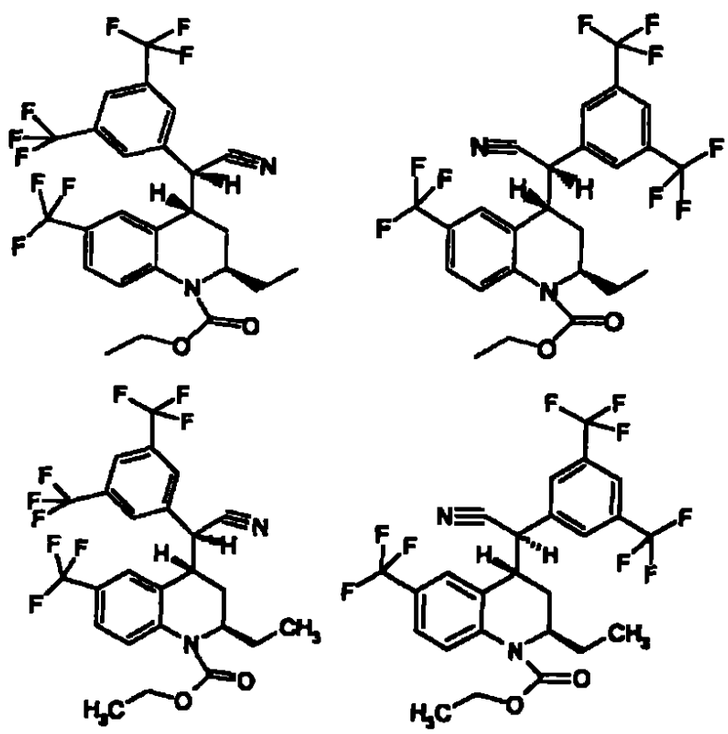
Éster etílico del ácido (*S*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico; o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 413 (Estereoisómeros de los Ejemplos 9 y 10)



Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, S, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico; Éster etílico del ácido (*S, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

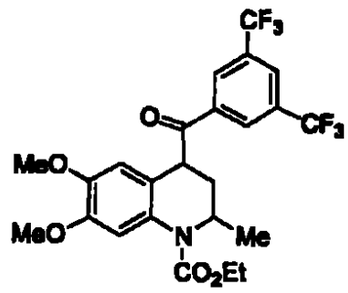
Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 414 (Estereoisómeros de los Ejemplos 13 y 14)



Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-benzoil)]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

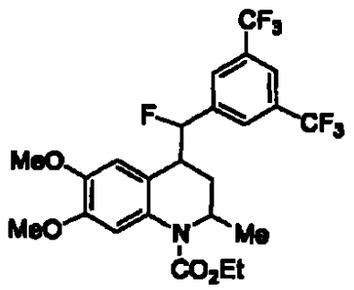
Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-benzoil)]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, R*)-4-[(3,5-bis-trifluorometil-benzoil)]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, S*)-4-[(3,5-bis-trifluorometil-benzoil)]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 415 (Estereoisómeros de los Ejemplos 18, 19 y 35)



Éster etílico del ácido (*R, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

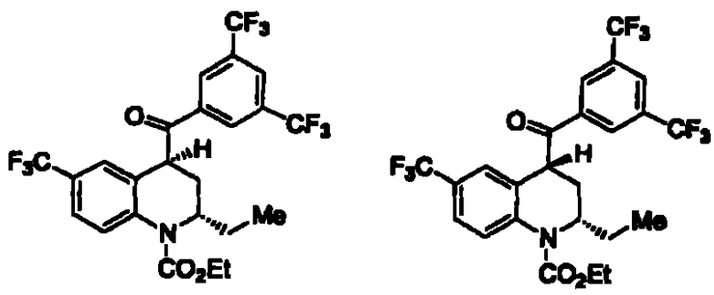
Éster etílico del ácido (*S, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, S, R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 416 (Estereoisómeros de los Ejemplos 20 y 21)

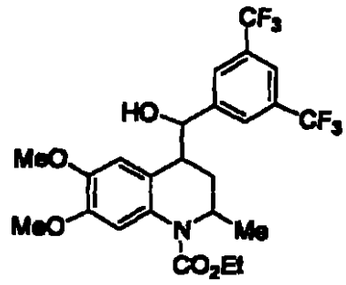


Éster etílico del ácido (*S, R*)-4-[(3,5-bis-trifluorometil-benzoil)]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico; o

Éster etílico del ácido (*S, S*)-4-[(3,5-bis-trifluorometil-benzoil)]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable del mismo.

Ejemplo 417 (Estereoisómeros de los Ejemplos 16 y 17)



Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

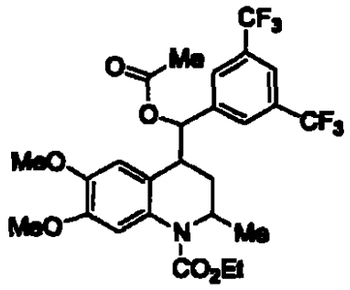
Éster etílico del ácido (*S*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 418 (Estereoisómeros del Ejemplo 34)



Éster etílico del ácido (*R*, *S*, *S*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *S*, *S*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

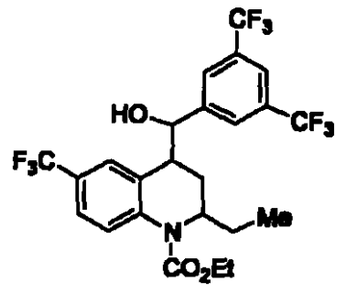
Éster etílico del ácido (*S*, *R*, *S*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (S, *S*, *R*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *R*, *R*)-4-[acetoxi-(3,5-bis-trifluorometil-fenil)-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 419 (Estereoisómeros de los Ejemplos 23, 23, 24 y 25)



Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

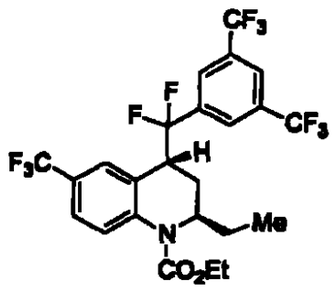
Éster etílico del ácido (*S*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 420



Éster etílico del ácido 4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

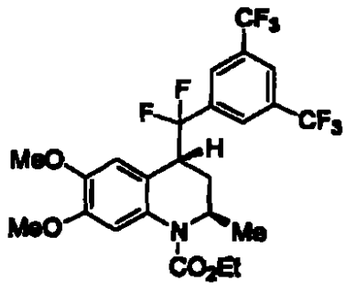
Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 421 (Estereoisómeros del Ejemplo 15)



Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6,7-dimetoxi-3,4-dihidro-2*H*-quinolin-1-carboxílico;

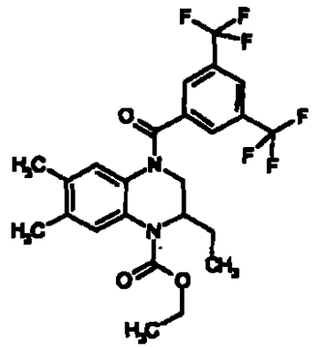
Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6,7-dimetoxi-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, R*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6,7-dimetoxi-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*S, S*)-4-[(3,5-bis-trifluorometil-fenil)-difluoro-metil]-2-etil-6,7-dimetoxi-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 422 (Estereoisómeros del Ejemplo 182)

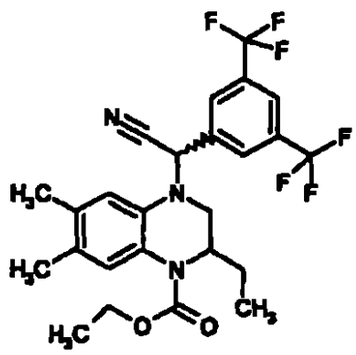


Éster etílico del ácido (*R*)-4-[(3,5-bis-trifluorometil-benzoil)]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico; o

Éster etílico del ácido (*S*)-4-[(3,5-bis-trifluorometil-benzoil)]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 423 (Estereoisómeros del Ejemplo 178)



Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

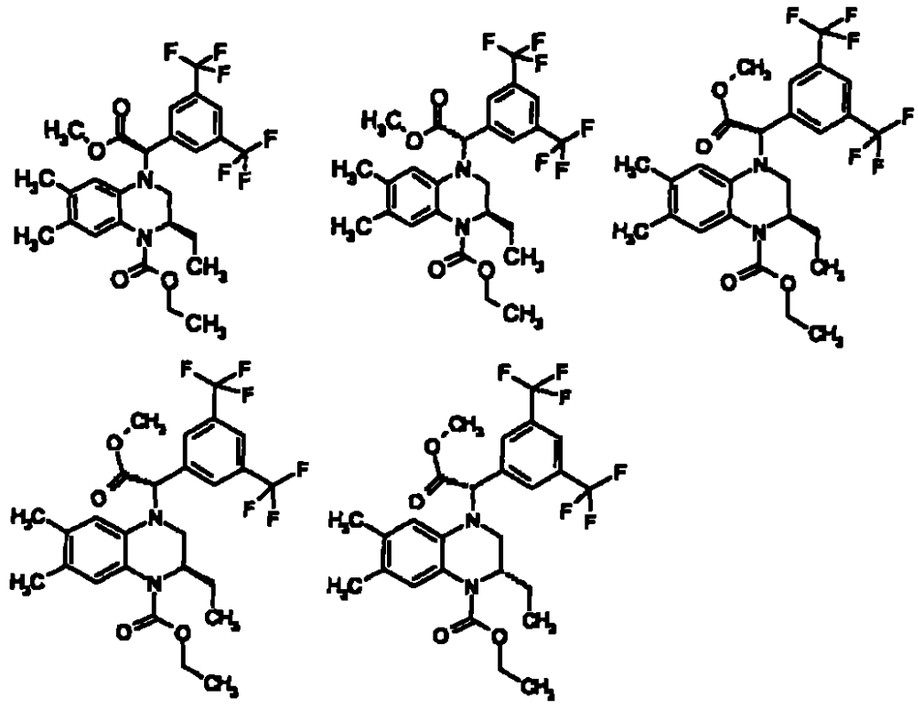
Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 424 (Estereoisómeros de los Ejemplos 170, 171, 172 y 173)



Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

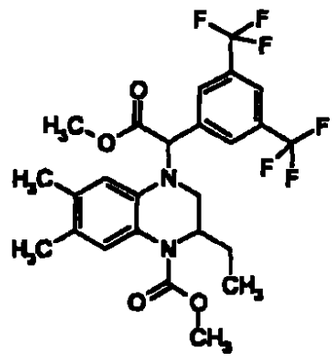
Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 425 (Estereoisómeros de los Ejemplos 174 y 175)



Éster metílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

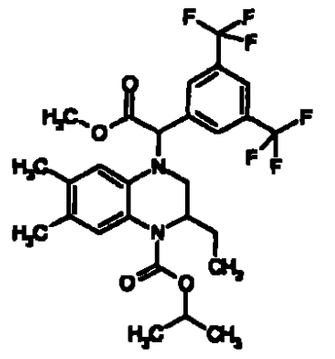
Éster metílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster metílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster metílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 426 (Estereoisómeros de los Ejemplos 176 y 177)



Éster isopropílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-

metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

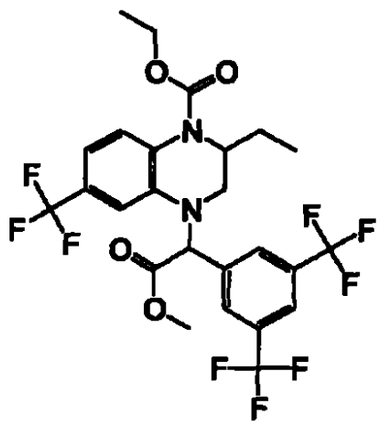
Éster isopropílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster isopropílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster isopropílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplo 427 (Estereoisómeros del Ejemplo 183)



Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

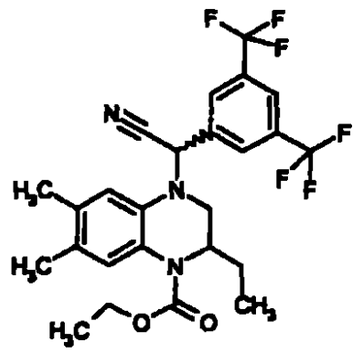
Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Ejemplos 428 y 429



Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico y éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico

Una mezcla de éster etílico del ácido 2-etil-6,7-dimetil-3,4-dihidro-2(R)-*H*-quinoxalin-1-carboxílico (1 g, 1 eq, 3,81 mmol), 3,5-bis-(trifluorometil-fenil)-bromo-acetonitrilo (Preparación 40, 1,27 g, 1 eq, 3,81 mmol) y 2,6-lutidina (3 eq, 11,43 mmol) en N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante 24 horas. La reacción se repartió entre acetato de etilo y agua y las fases se separaron. La fase acuosa se extrajo 3 veces con acetato de etilo y los extractos orgánicos combinados se lavaron 2 veces con agua, 1 vez con salmuera, se secaron sobre sulfato sódico anhidro, se filtraron y se evaporaron. La cromatografía en gel de sílice usando un gradiente de 10-30% de acetato de etilo en hexanos como eluyente proporcionó los diastereoisómeros del nitrilo deseado (1,5:1) (1,0 g y 0,7 g, 60%).

Isómero 1:

LCMS (ESI+): 514 (MH+)

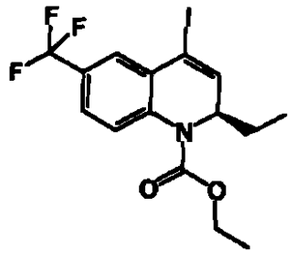
^{1}H RMN ($CDCl_3$): □ 0,88 (y, J = 7,5 Hz, 3H), 1,29 (t, J = 7,1 Hz, 3H), 1,49 (m, 2H), 2,21 (s, 3H), 2,22 (s, 3H), 3,03 (dd, J = 11,0 Hz, J_2 = 2,9 Hz, 1H), 3,19 (dd, J_1 = 11,0 Hz, J_2 = 5,4 Hz, 1H), 4,19 (m, 1H), 4,27 (m, 1H), 4,50 (m a, 1H), 6,05 (s, 1H), 6,59 (s, 1H), 7,33 (s a,1H), 7,94 (s, 1H), 7,97 (s, 2H).

Isómero 2:

LCMS (ESI+): 514 (MH+)

^{1}H RMN ($CDCl_3$) □ 0,76 (t, J = 7,48 Hz, 3H), 1,31 (t, J = 7,06 Hz, 3H), 1,52 (m, 2H), 2,21 (s, 3H), 2,23 (s, 3H), 2,75 (dd, J_1 = 11,0 Hz, J_2 = 2,1 Hz, 1H), 3,29 (dd, J_1 = 11,0 Hz, J_2 = 3,73 Hz, 1H), 4,19-4,30 (m, 2H), 4,52 (m a, 1H), 6,19 (s, 1H), 6,70 (s, 1H), 7,47 (s a, 1H), 7,96 (s, 1H), 8,00 (s, 2H).

Preparación 42



Éster etílico del ácido (*R*)-2-etil-4-yodo-6-trifluorometil-2*H*-quinolin-1-carboxílico

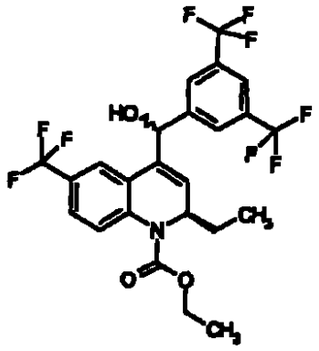
El compuesto del título se preparó usando el procedimiento general descrito por D.H.R Barton et al. (Tetrahedron Letters 1983 *24*, 1605). A una solución de yodo (3,0 g, 9,1 mmol) en tetrahidrofurano anhidro (30 ml) en una atmósfera de nitrógeno se le añadió lentamente una solución de 1,1,3,3-tetrametilguanidina(63,7 mmol, 8ml) en tetrahidrofurano anhidro (30 ml). La mezcla se agitó a temperatura ambiente durante 10 minutos antes de añadir éster etílico del ácido (*R*)-2-etil-4-hidrazono-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 6, 9,1 mmol, 3 g) en tetrahidrofurano anhidro. Después de 15 minutos el disolvente se retiró al vacío y el

residuo se calentó en una atmósfera de nitrógeno a 85°C durante 90 minutos. El residuo se disolvió en acetato de etilo, se lavó con ácido clorhídrico 2N, solución acuosa de sulfito sódico (2,5%), solución saturada de hidrogenocarbonato sódico y se secó sobre sulfato sódico anhidro. El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con hexanos/acetato de etilo de 19:1 a 85:15 para dar el compuesto del título en forma de sólido amarillo (2,8 g, 72%).

MS: 426,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,69 (s a,1H), 7,61 (d a, J = 8,14 Hz, 1H), 7,49 (d a, J = 8,14 Hz, 1H), 6,85 (d, J = 6,64 Hz, 1H), 4,87 (m, 1H), 4,27 (m, 2H), 4,15 (m, 1H), 1,50 (m, 1H), 1,38 (m, 1H), 1,32 (t, J = 7,47 Hz, 3H), 0,87 (t, J = 7,47 Hz, 3H).

Ejemplo 430



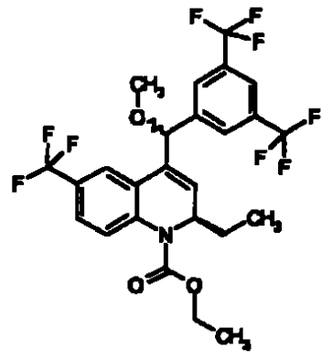
Éster etílico del ácido (*RS, RS*) y (*RS, SR*)-4-[(3,5-bis-trifluoro-metil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*RS*)-2-etil-4-yodo-6-trifluorometil-2*H*-quinolin-1-carboxílico (814 mg, 1,91 mmol, preparado como se ha descrito anteriormente para el isómero (*R*) excepto que se usó el material de partida racémico) en tetrahidrofurano anhidro (4 ml) en una atmósfera de nitrógeno a -78°C se le añadió gota a gota n-butillitio (2,5M en hexanos, 2,87 mmol, 1,15 ml). Después de 5 minutos se añadió gota a gota bis(trifluorometil)benzaldehído (6,06 mmol, 1 ml). Después de 45

minutos a -78°C la mezcla se dejó calentar a temperatura ambiente y después de una hora se añadió agua. La mezcla se acidificó por adición de ácido clorhídrico 2N y se extrajo con acetato de etilo. La solución orgánica se lavó con agua, se secó sobre sulfato sódico anhidro y se evaporó al vacío. El residuo se purificó por cromatografía en gel de sílice eluyendo con hexanos/acetato de etilo de 9:1 a 4:1 y después se purificó adicionalmente por cromatografía en gel de sílice eluyendo con diclorometano para dar los compuestos del título en forma de una mezcla de diastereoisómeros (60 mg).

MS: 540,3 $[M+H]^+$ encontrado

Ejemplo 431

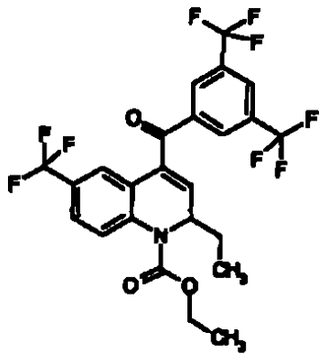


Éster etílico del ácido (*RS, RS*) y (*RS, SR*)-4-[(3,5-bis-trifluorometil-fenil)-metoxi-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de la mezcla diastereoisómerica éster etílico del ácido (*RS, RS*) y (*RS, SR*)-4-[(3,5-bis-trifluoro-metil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (Ejemplo 430, 32 mg, 0,059 mmol) en dimetilsulfóxido (3 ml) en una atmósfera de nitrógeno se le añadió hidróxido de potasio en polvo (0,236 mmol, 13 mg) seguido inmediatamente de yodometano (0,118 mmol, 7,4 µl). La mezcla se agitó a temperatura ambiente durante 2 horas y después se diluyó con ácido clorhídrico 2N. La mezcla se extrajo con acetato de etilo, la capa orgánica se lavó con agua y solución saturada de cloruro sódico, se secó sobre sulfato sódico anhidro y se evaporó al vacío.

El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con hexanos, después con hexanos/acetato de etilo, después 19:1 y después 85:15 para dar el compuesto del título (13 mg) en forma de una mezcla de diastereoisómeros.

Ejemplo 432



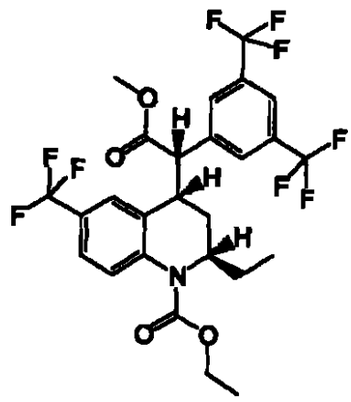
Éster etílico del ácido (*RS*)-4-[(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de la mezcla diastereoisomérica éster etílico del ácido (*RS, RS*) y (*RS, SR*)-4-[(3,5-bis-trifluoro-metil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (Ejemplo 430, 11 mg, 0,020 mmol) en éter dietílico anhidro (1 ml) se le añadió óxido de manganeso (IV) (22 mg, activado, ~85%, Aldrich Chemical Company, Milwaukee, WI). La suspensión se agitó a temperatura ambiente durante 90 minutos. Se añadió un segundo alícuota de óxido de manganeso (IV) (20 mg) y se siguió agitando durante una hora más antes de añadir un tercer alícuota de óxido de manganeso (IV). Después de 10 minutos, el sólido se retiró por filtración a través de Celite ®, el disolvente se retiró al vacío y el residuo se cromatografió en gel de sílice Baker (1 g, 40 μm) (J.T. Baker, Phillipsburg, N.J.) eluyendo con hexanos, después hexanos/acetato de etilo 19:1, después 9:1, después 85:15 y después 4:1 para dar el compuesto del título (6,6 mg).

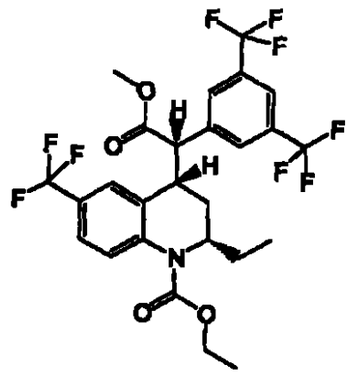
MS: 540,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 8,27 (s, 2H), 8,11 (s, 1H), 7,79 (d a, J = 8,3 Hz, 1H), 7,77 (s a, 1H), 7,57 (d a, J = 8,3 Hz, 1H), 6,56 (d, J = 6,64 Hz, 1H), 5,18 (m, 1H), 4,31 (m, 2H), 1,64 (m, 1H), 1,55 (m, 1H), 1,33 (t, J = 7,47 Hz, 3H), 0,96 (t, J = 7,47 Hz, 3H).

Ejemplos 433 y 434



Éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*S, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se resolvió éster etílico del ácido (*RS, RS, SR*) 4-[(3,5-bis-trifluorometil-fenil)-

metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (ejemplo 7) en una columna Pirkle Covalent (S,S) Whelk-O 1 (Regis Technologies, Inc., Morton Grove, IL) (5x25 cm) eluyendo a 100 ml/min con etanol al 5%/heptano para proporcionar dos fracciones.

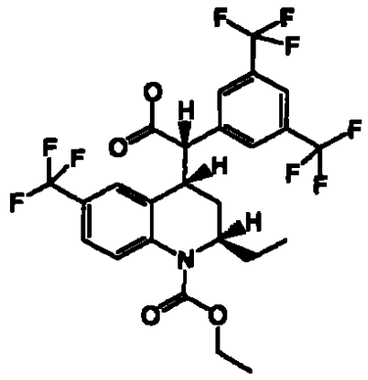
Eluye en primer lugar: Éster etílico del ácido (*S, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

MS: 585,8 $[M+H]^+$ encontrado.

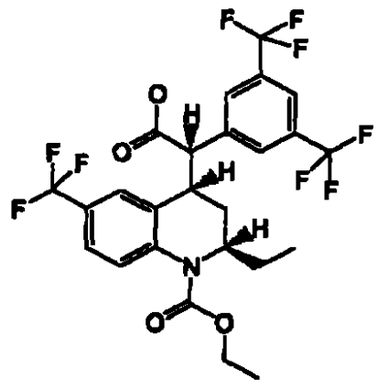
Eluye en segundo lugar: Éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

MS: 586,2 $[M+H]^+$ encontrado.

Ejemplos 435 y 436



Éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, R, R*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 433, 98 mg, 0,167 mmol), hidróxido sódico acuoso (1N, 1 ml, 1 mmol) y tetrahidrofurano anhidro (2,4 ml) se agitó a temperatura ambiente durante 5 días antes de añadir ácido clorhídrico 2N hasta pH ácido. La mezcla se extrajo con acetato de etilo, la solución orgánica se lavó con agua (x3) y se secó sobre sulfato sódico anhidro. El disolvente se retiró al vacío y el residuo se cromatografió en gel de sílice Baker (1 g, 40 μM) (J.T. Baker, Philippsburg, NJ) eluyendo con un gradiente de hexanos-acetato de etilo de 0% a 80% para dar los compuestos del título.

Eluye en primer lugar: Éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (67 mg);

MS: 572,4 $[M+H]^+$ encontrado.

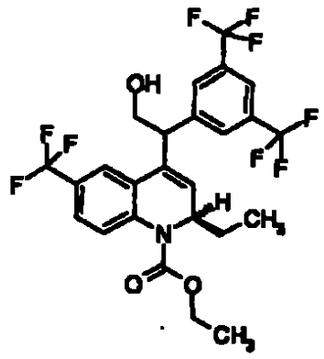
^{1}H RMN ($CDCl_3$) □ 7,9 0(s, 1H), 7,89 (s, 2H), 7,54 (m, 2H), 7,46 (s a, 1H), 4,28 (m, 2H), 4,22 (m, 1H), 4,08 (d, J = 11,2 Hz, 1H), 3,37 (m, 1H), 1,76 (m, 1H), 1,48 (m, 1H), 1,38 (m, 1H), 1,31 (t, J = 7,05 Hz, 3H), 0,95 (m, 1H), 0,70 (t, J = 7,47 Hz, 3H).

Eluye en segundo lugar: Éster etílico del ácido (*R*, *R*, *R*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (29,5 mg);

MS: 572,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$): □ 7,94 (s, 2H), 7,83 (s, 1H), 7,50(d, J = 8,14 Hz, 1H), 7,41 (d a, J = 8,14 Hz, 1H), 7,0 1(s a, 1H), 4,42 (m, 1H), 4,22 (m, 2H), 4,21 (m, 1H), 3,32 (m, 1H), 2,45 (m, 1H), 1,58 (m, 1H), 1,41 (m, 1H), 1,41 (m, 1H), 1,28 (t, J = 7,47 Hz, 3H), 0,79 (t, J = 7,47 Hz, 3H).

Ejemplo 437



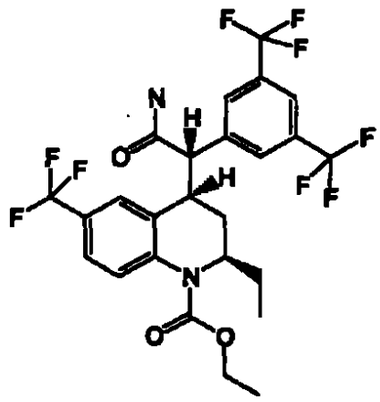
Éster etílico del ácido (*R*, *R'*) y (*R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*R*,*R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico y éster etílico del ácido (*R*,*S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (ejemplos 3 y 4, usados en forma de mezcla obtenida antes de la separación, 329 mg, 0,563 mmol) en tetrahidrofurano anhidro (6 ml) en una atmósfera de nitrógeno a -40°C se le añadió gota a gota una solución de hidruro de aluminio litio (1M en tetrahidrofurano, 845 µl, 0,845 mmol). Después de 30 minutos se añadió un exceso de acetato de etilo para inactivar la reacción y la mezcla se

dejó calentar a temperatura ambiente. La mezcla se agitó con agua/acetato de etilo, la capa orgánica se lavó con agua, se secó sobre sulfato sódico anhidro y se evaporó al vacío. El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con hexanos, después hexanos/acetato de etilo 9:1, después 4:1 y después 7:3 para dar los compuestos del título en forma de una mezcla de diastereoisómeros (243 mg).

MS: 556,3 $[M+H]^+$ encontrado.

Ejemplo 438



Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 435, 110 mg, 0,193 mmol) y cloruro de tionilo (1 ml) se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 3 días y después se retiró el exceso de cloruro de tionilo (1 ml) al vacío. Al residuo se le añadió una solución de amoniaco en dioxano (0,5M, 6 ml, 3 mmol). Después de 12 horas, la mezcla se diluyó con acetato de etilo, se lavó con agua (x2), la capa orgánica se secó sobre sulfato sódico anhidro y después s evaporó a sequedad al vacío. El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con diclorometano/acetato de etilo 39:1, después 19:1 para dar el

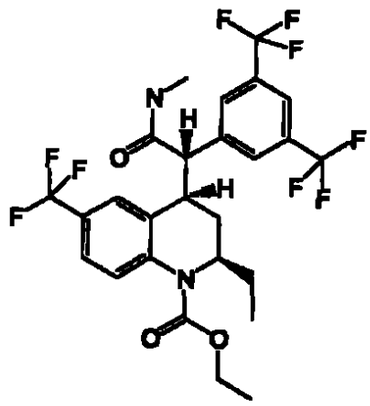
compuesto del título (103 mg).

MS: 571,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,88 (s, 1H), 7,88 (s, 2H), 7,51 (m, 2H), 7,46 (s a, 1H), 5,80 (s a, 1H), 5,53 (s a, 1H), 4,26 (m, 1H), 4,26 (m, 1H), 4,19 (m ,1H), 3,82 (d, J = 10,79 Hz, 1H), 3,45 (m, 1H), 1,68 (m, 1H), 1,49 (m ,H), 1,39 (m, 1h), 1,29 (t, J = 7,06 Hz, 3H), 0,95 (m, 1H), 0,70 (t, J = 7,47 Hz, 3H).

Los dos siguientes compuestos se prepararon con procedimientos análogos utilizando, respectivamente, metilamina y dimetilamina en lugar de amoniaco:

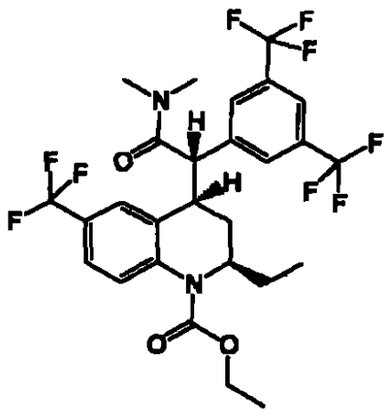
Ejemplo 439



Éster etílico del ácido (*R, R, S)*-4-[(3,5-bis-trifluorometil-fenil)-metilcarbamoil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 585,3 $[M+H]^+$ encontrado.

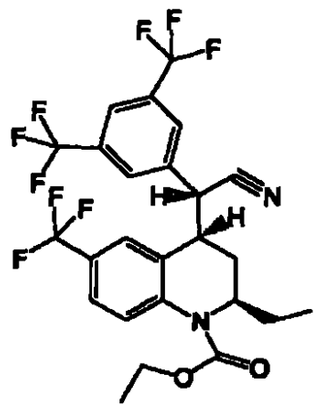
Ejemplo 440



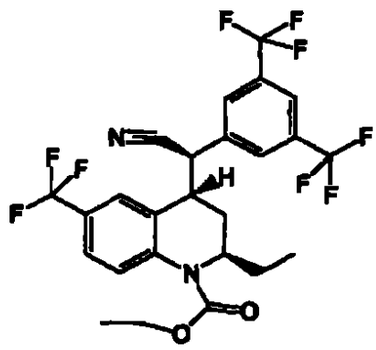
Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-dimetilcarbamoil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 599,3 $[M+H]^+$ encontrado.

Ejemplos 441 y 442



Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico(Ejemplo 438, 30 mg, 0,053 mmol) en diclorometano anhidro (1 ml) se le añadió hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess, 37 mg, 0,157 mmol). La mezcla se agitó a temperatura ambiente durante 72 horas en una atmósfera de nitrógeno y después se evaporó al vacío. El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con hexanos, después con hexanos/acetato de etilo 19:1 y después 9:1 para dar los compuestos del título:

Eluye en primer lugar: Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (8 mg);

MS: 555,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,96 (s, 1H), 7,90 (s, 2H), 7,60 (m, 2H), 7,56 (s a, 1H), 4,88 (d, J = 3,32 Hz, 1H), 4,28 (m, 1H), 4,22 (m, 1H), 4,22 (m, 1H), 2,93 (m, 1H), 2,22 (m, 1H), 1,63 (m, 1H), 1,62 (m, 1H), 1,51 (m, 1H), 1,27 (t, J = 7,47 Hz, 3H), 0,83 (t, J = 7,47 Hz, 3H).

Eluye en segundo lugar: Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-

carboxílico (20 mg);

MS: 553,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$): □ 7,96 (s, 1H), 7,92 (s, 2h), 7,59 (s a, 1H), 7,57 (m, 2H), 4,36 (m, 1H), 4,30 (m, 1H), 4,27 (d, J = 8,3 Hz, 1H), 4,22 (m, 1H), 3,23 (m, 1H), 2,08 (m, 1H), 1,55 (m, 1H), 1,43 (m, 1H), 1,30 (t, J = 7,47 Hz, 3H), 1,27 (m, 1H), 0,79 (t, J = 7,47 Hz, 3H).

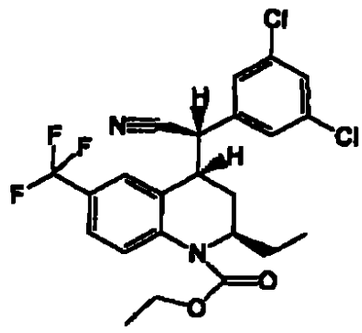
Preparación 43

Éster etílico del ácido (*R*)-4-bromo-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

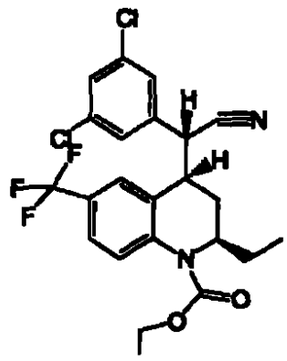
A una solución de éster etílico del ácido (*R,S*)-2-etil-4-hidroxi-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 13, 3,29 g, 10,37 mmol) en diclorometano (25 ml) a temperatura ambiente en una atmósfera de nitrógeno se le añadió piridina (1,58 ml) seguido de una solución de bromuro de fósforo (III) gota a gota (1,1 ml) en diclorometano (10 ml). La mezcla se dejó agitar a temperatura ambiente durante 15 horas y después se repartió entre agua y diclorometano. La capa orgánica se lavó con una solución saturada de hidrogenocarbonato sódico (2 x 15 ml), se secó sobre sulfato sódico anhidro y el disolvente se retiró a presión reducida para dar el compuesto del título en forma de un aceite amarillo (3,79 g) que contenía una mezcla aproximadamente 5:1 de diastereoisómeros y una cantidad variable de éster etílico del ácido (*R*)-2-etil-6-trifluorometil-2*H*-quinolín-1-carboxílico formado por eliminación de bromuro de hidrógeno. El bromuro en bruto se usó directamente sin purificación adicional o se almacenó en el refrigerador para evitar la descomposición adicional.

MS: 379, 381 $[M]^{.+}$ encontrado (GC-MS).

Ejemplos 443 y 444



Éster etílico del ácido (*R, R, R*) 4-[ciano-(3,5-dicloro-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, R, S*) 4-[ciano-(3,5-dicloro-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

A una solución de 3,5-diclorofenilacetonitrilo (134 mg, 0,72 mmol, preparado de acuerdo con el procedimiento descrito en el documento WO00/58292) en N,N-dimetilformamida anhidro (1 ml) se le añadió hidruro sódico (dispersión en aceite mineral al 60%, 0,925 mmol, 37 mg) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se añadió una solución de éster etílico del ácido (*R*)-4-bromo-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Preparación 43, 250 mg, mezcla de isómeros como se ha preparado anteriormente) en N,N-dimetilformamida

anhidro (1,5 ml) y la mezcla se agitó a temperatura ambiente durante 5 minutos. Se añadió agua y la mezcla se extrajo con éter dietílico (3x20 ml) y el extracto orgánico se diluyó con heptano y se evaporó a sequedad para dar el producto en bruto en forma de aceite amarillo (~400 mg). La purificación inicial se realizó por cromatografía en gel de sílice eluyendo con hexanos/acetato de etilo 9:1. Las fracciones que contenían los compuestos del título se purificaron adicionalmente usando cromatografía radial (Chromatron modelo 7924T, Harrison Research, Palo Alto, CA) con un rotor de gel de sílice de 2mm eluyendo con hexanos/acetato de etilo 9:1 para dar los compuestos del título.

Eluye en primer lugar:

Éster etílico del ácido (*R, R, R*) 4-[ciano-(3,5-dicloro-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

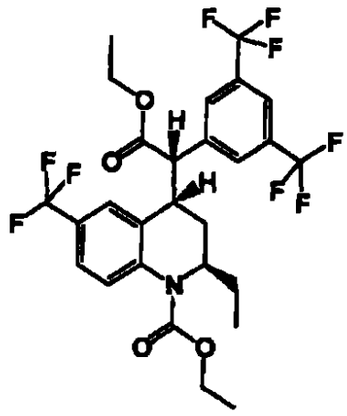
^{1}H RMN ($CDCl_3$) □ 7,59 (s, 2h), 7,54 (s, 1H), 7,43 (t, J = 1,95 Hz, 1H), 7,35 (d, J = 1,95 Hz, 2H), 4,69 (d, J = 3,52 Hz, 1H), 4,28 (m, 1H), 4,22 (m, 1H), 4,22 (m, 1H), 2,90 (m, 1H), 2,27 (m, 1H), 1,61 (m, 1H), 1,50 (m, 1H), 1,49 (m, 1H), 1,29 (t, J = 7,03 Hz, 3H), 0,84 (t, J = 7,42 Hz, 3H).

Eluye en segundo lugar: Éster etílico del ácido (*R, R, S*) 4-[ciano-(3,5-dicloro-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

MS: 485,2 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,59 (s, 1H), 7,55 (s, 2H), 7,42 (t, J = 1,66 Hz, 1H), 7,33 (d, J = 1,66 Hz, 2H), 4,34 (m, 1H), 4,27 (m, 1H), 4,22 (m, 1H), 4,01 (d, J = 9,13 Hz, 1H), 3,13 (m, 1H), 2,07 (m, 1H), 1,53 (m, 1H), 1,42 (m, 1H), 1,30 (t, J = 7,47 Hz, 3H), 1,16 (m, 1H), 0,78 (t, J = 7,47 Hz, 3H).

Ejemplo 445



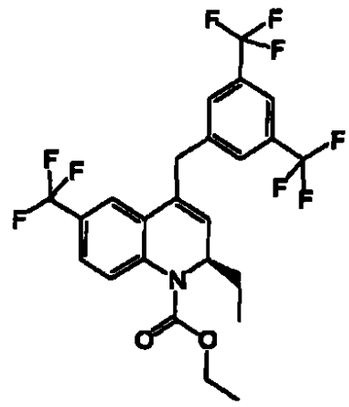
Éster etílico del ácido (*R*, *R*, *S*) 4-[(3,5-bis-trifluorometil-fenil)-etoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido (*R*, *R*, *S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 435, 33 mg, 0,058 mmol) en etanol anhidro (5 ml) que contenía ácido sulfúrico concentrado (4 gotas) se calentó a reflujo durante 18 horas y después el disolvente se evaporó al vacío. El residuo se repartió entre agua y acetato de etilo, la capa orgánica se lavó con agua, se secó sobre sulfato sódico anhidro y se evaporó al vacío. El residuo se purificó por cromatografía en gel de sílice eluyendo con hexanos y después con un gradiente de hexanos/acetato de etilo de 9:1 a 4:6 para dar el compuesto del título (17,5 mg) en forma de goma.

MS: 600,6 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,88 (s, 2H), 7,88 (s, 1H), 7,53 (m, 2H), 7,44 (s a, 1H), 4,35 (m, 1H), 4,27 (m, 2H), 4,22 (m, 1H), 4,06 (m, 1H), 4,01 (d, J = 11,62 Hz, 1H), 3,37 (m, 1H), 1,73 (m, 1H), 1,48 (m, 1H), 1,38 (m, 1H), 1,30 (t, J = 7,06 Hz, 3H), 1,27 (t, J = 7,06 Hz, 3H), 0,94 (m, 1H), 0,70 (t, J = 7,47 Hz, 3H).

Ejemplo 446



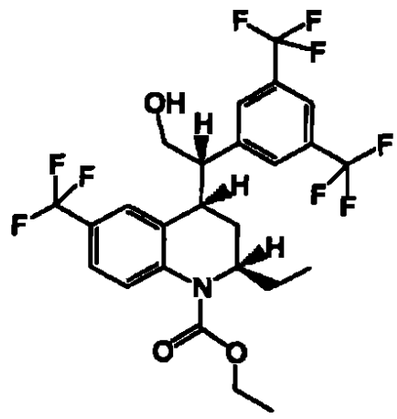
Éster etílico del ácido (*R*)-4-[(3,5-bis-trifluorometil-bencil)-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*R,R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico y éster etílico del ácido (*R,S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (Ejemplos 3 y 4, usado en forma de una mezcla de diastereoisómeros antes de la separación, 148 mg, 0,253 mmol) en tetrahidrofurano (3 ml) en una atmósfera de nitrógeno se le añadió una solución acuosa de hidróxido sódico (1M, 250 µl, 0,25 mmol). Después de agitar a temperatura ambiente durante 72 horas se añadió un alícuota adicional de solución acuosa de hidróxido sódico (1M, 100 µl, 0,1 mmol). Después de 72 horas, la mezcla se acidificó por adición de ácido clorhídrico 2N y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato sódico anhidro, se evaporó al vacío y el residuo se purificó por cromatografía en gel de sílice eluyendo con diclorometano/hexanos 1:1, después 3:1, seguido de diclorometano y después diclorometano/metanol 9:1, después un gradiente de hexanos/acetato de etilo de 9:1 a 4:6 para dar el compuesto del título (4,5 mg).

MS: 526,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,76 (s, 1H), 7,74 (m, 1H), 7,68 (s, 2H), 7,48 (m, 1H), 7,42 (s a, 1H), 5,76 (d, J = 5,81 Hz, 1H), 4,93 (m, 1H), 4,27 (m, 2H), 3,92 (m, 1H), 3,88 (m, 1H), 1,48 (m,1 H), 1,38 (m, 1H), 1,32 (t, J = 7,47 Hz, 3H), 0,85 (t, J = 7,47 Hz, 3H).

Ejemplo 447



Éster etílico del ácido (*R, R, S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 435, 67 mg, 0,117 mmol) en tetrahidrofurano (1 ml) en una atmósfera de nitrógeno se le añadió un complejo de borano-dimetilsulfuro (22,2 µl, 0,234 mmol). Después de 24 horas se añadió hidróxido sódico acuoso (1M, 4 gotas) para inactivar la reacción y la mezcla se dejó agitar durante 1 hora. La mezcla se acidificó por adición de ácido clorhídrico 2N, se agitó durante 10 minutos y se extrajo con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato sódico anhidro y el disolvente se evaporó al vacío. El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con hexanos, después hexanos/acetato de etilo 19:1, después 9:1, después 4:1, después 3:7 y por último 2:3 para dar el compuesto del título (54 mg).

MS: 558,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,83 (s, 1H), 7,80 (s, 2H), 7,60 (s a, 1H), 7,52 (m, 2H), 4,27 (m, 1H), 4,24 (m, 2H9, 4,20 (m, 1H), 4,00 (m, 1H), 3,54 (m, 1H), 2,84 (m, 1H), 1,82 (m, 1H), 1,63 (s a, 1H), 1,46 (m, 1H), 1,32 (m, 1H), 1,31 (t, J = 7,05 Hz, 3H), 0,87 (m, 1H), 0,69 (t, J = 7,447 Hz, 3H).

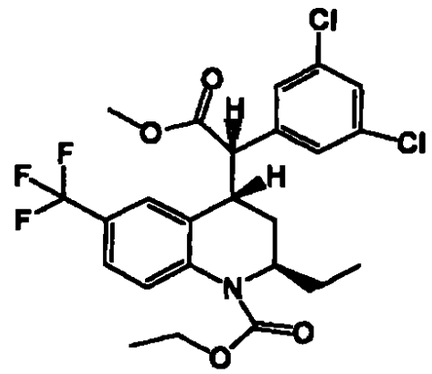
Preparación 44

(3,5-dicloro)-fenilacetato de metilo

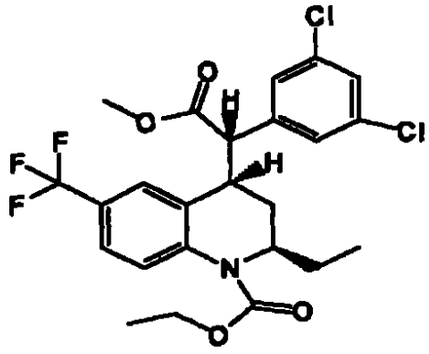
Una mezcla de 3,5-diclorofenilacetonitrilo (2 g, preparado de acuerdo con el procedimiento descrito en el documento WO00/58292), etanol (25 ml), hidróxido de potasio (3,95 g) y agua (10 ml) se calentó a reflujo durante 4 horas y después se evaporó a sequedad al vacío. El residuo se repartió entre agua (20 ml) y éter dietílico y la capa acuosa se acidificó a pH 1 por adición de ácido clorhídrico concentrado. La mezcla se extrajo con éter dietílico (3 x 25 ml), la capa orgánica se secó sobre sulfato sódico anhidro y se evaporó al vacío. El ácido carboxílico se disolvió en metanol (20ml) y se añadió lentamente trimetilsilildiazometano (solución 2M en hexanos, 30 ml, Aldrich Chemical Company, Milwaukee, WI). Después de 1 hora, el disolvente se retiró al vacío, el residuo se disolvió en éter dietílico, se lavó con una solución acuosa de carbonato sódico (2M) se secó sobre sulfato sódico anhidro y se evaporó a sequedad para dar el compuesto del título (2,1 g).

^{1}H RMN ($CDCl_3$) □ 7,27 (s, 1H), 7,17 (s, 2H), 3,71 (s, 3H), 3,57 (s, 2H).

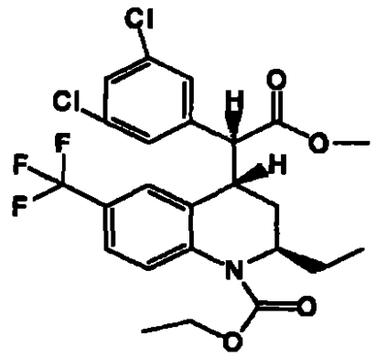
Ejemplos 448, 449, 450 y 451



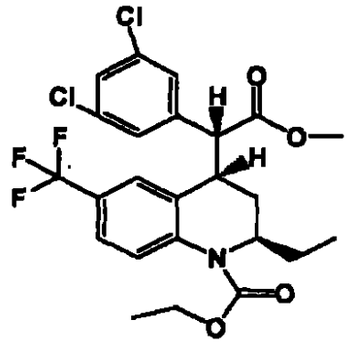
Éster etílico del ácido (*R, S, R*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, R, S*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, S, S*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, R, R*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

A una solución de (3,5-dicloro)-fenilacetato de metilo (311 mg, 1,42 mmol) en N,N-dimetilformamida anhidro (3 m) se le añadió hidruro sódico (dispersión en aceite mineral al 60%, 1,93 mmol, 77 mg) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se añadió una solución de éster etílico del ácido (*R*) 4-bromo-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (490 mg, mezcla de isómeros, Preparación 43) en N,N-dimetilformamida anhidro (5 ml) y la mezcla se agitó a temperatura ambiente durante 5 minutos. Se añadió agua y la mezcla se extrajo con éter dietílico (3 x 20 ml) y el extracto orgánico se diluyó con heptano y se evaporó a

sequedad para dar el producto en bruto en forma de aceite amarillo (~460 mg). La purificación inicial se realizó por cromatografía usando cromatografía radial (Chromatron modelo 7924T, Harrison Research, Palo Alto, CA) con un rotor de gel de sílice de 4 mm eluyendo con hexanos/acetato de etilo 9:1 y recromatografiando posteriormente las fracciones apropiadas eluyendo con diclorometano/hexanos 45:55 para dar los compuestos del título:

Éster etílico del ácido (*R, S, R*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 518,3 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$): □ 7,55 (d a, J = 8,30 Hz, 1H), 7,49 (d a, J = 8,30 Hz, 1H), 7,48 (s a, 1H), 7,33 (m, 2H), 7,33 (m, 1H), 4,33 (m, 1H), 4,31 (m, 1H), 4,24 (m, 1H), 3,56 (d, J = 11,62 Hz, 1H), 3,52 (m, 1H), 3,46 (s, 3H), 1,86 (m, 1H), 1,53 (m, 1H), 1,46 (m, 2H), 1,34 (t, J = 7,47 Hz, 3H), 0,74 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*R, R, S*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 518,3 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$): □ 7,52 (m, 1H), 7,50 (m, 1H), 7,35 (t, J = 1,66 Hz, 1H), 7,32 (s a, 1H), 7,30 (d, J = 1,66 Hz, 2H), 4,30 (m, 1H), 4,27 (m, 1h), 4,20 (m, 1H), 3,78 (d, J = 11,61 Hz, 1H), 3,74 (s, 2H), 3,28 (m, 1H), 1,85 (m, 1H), 1,49 (m, 1H), 1,39 (m, 1H), 1,30 (t, J = 7,47 Hz, 3H), 0,91 (m, 1H), 0,72 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*R, S, S*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 518,3 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$): □ 7,43 (d, J = 8,30 Hz, 1H), 7,36 (dd, J = 8,30, 1,66 Hz, 1H), 7,15 (t, J = 1,66 Hz, 1H), 6,88 (d, J = 1,66 Hz, 2H), 6,69 (s a, 1H), 4,45 (m, 1H), 4,32

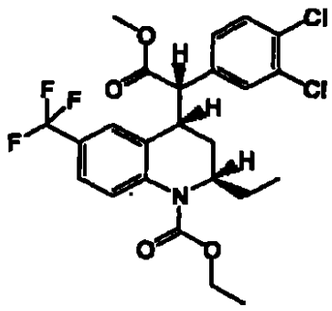
(m, 1H), 4,31 (m, 1H), 3,75 (s, 3H), 3,62 (d, J = 10,79 Hz, 1H), 3,40 (m, 1H), 2,88 (m, 1H), 1,75 (m, 1H), 1,64 (m, 1H), 1,48 (m, 1H), 1,34 (t, J = 7,46 Hz, 3H), 0,83 (t, J = 7,4 Hz, 3H).

Éster etílico del ácido (*R, R, R*) 4-[(3,5-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 518,3 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$): □ 7,51 (d a, J = 8,59 Hz, 1H), 7,43 (s a, J = 8,59 Hz, 1H), 7,33 (m, 2H), 7,31 (m, 1H), 7,10 (s a, 1H), 4,40 (m, 1H), 4,28 (m, 1H), 4,23 (m, 1H), 4,06 (d, J = 10,15 Hz, 1H), 3,74 (s, 2H), 3,24 (m, 1H), 2,32 (m, 1H), 1,64 (m, 1H), 1,47 (m, 1H), 1,37 (m, 1H), 1,32 (t, J = 7,02 Hz, 3H), 0,83 (t, J = 7,47 Hz, 3H).

Ejemplo 452



Éster etílico del ácido (*R, R, S*)-4-[(3,4-dicloro-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

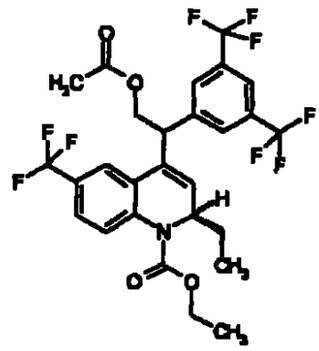
A una solución de (3,4-dicloro)-fenilacetato de metilo (1,22 g, 5,57 mmol) en N,N-dimetilformamida anhidro (5 ml) se le añadió hidruro sódico (dispersión al 60% en aceite mineral, 7 mmol, 280 mg) y la mezcla se agitó a temperatura ambiente durante 5 minutos. Se añadió una solución de éster etílico del ácido (*R*) 4-bromo-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (798 mg, mezcla de isómeros, Preparación 43) en N,N-dimetilformamida anhidro (4 ml) y la mezcla se agitó a

temperatura ambiente durante 15 minutos. Se añadió agua y la mezcla se acidificó por adición de ácido clorhídrico 2N y después se extrajo con éter dietílico (x3) y el extracto orgánico se diluyó con heptano y se evaporó a sequedad para dar el producto en bruto en forma de aceite amarillo. Este aceite se disolvió en tetrahidrofurano (10 ml) y agua (5 ml) y se añadió hidróxido sódico acuoso (2N, 10 ml). La mezcla se agitó a temperatura ambiente durante 24 horas y después se repartió entre ácido clorhídrico (0,1N) y diclorometano. El extracto orgánico se secó sobre sulfato sódico anhidro y se evaporó a sequedad para dar una mezcla de ácidos carboxílicos. Este material se purificó por cromatografía en gel de sílice eluyendo con hexanos/acetato de etilo 5:1 y después 4:1. Las fracciones que contenían el primer ácido carboxílico en eluir (con la estereoquímica deseada *R, R, S*) se combinaron, se evaporaron a sequedad al vacío y se disolvieron en metanol (25 ml). Se añadió lentamente trimetilsilildiazometano (solución 2M en hexanos, Aldrich Chemical Company, Milwaukee, WI) hasta que la efervescencia cesó y persistía un color amarillo. Esto se descargó por adición de una pequeña cantidad de ácido acético y el disolvente se retiró al vacío y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de hexanos/diclorometano de 2:1 a 1:2. La purificación final se realizó usando HPLC de fase inversa usando el sistema de HPLC preparativa de Shimadzu (Shimadzu Corporation, Kyoto, Japón) eluyendo con un gradiente de 30-100% acetonitrilo/agua/ácido fórmico al 0,1% en una columna de 19x50 mm Waters Symmetry (Waters Corp, Milford, MA) durante 8 minutos, gradiente 6 minutos, 25 ml/min, recogida disparada por UV, observancia a 210 nm. Las fracciones que contenían el producto se evaporaron a sequedad para dar el compuesto del título (75 mg).

MS: 518,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$): □ 7,52 (m, 1H), 7,51 (m, 1H), 7,50 (m, 1H), 7,47 (d, J = 8,3 Hz, 1H), 7,34 (s a, 1H), 7,25 (dd, J = 8,3, 2,49 Hz, 1H), 4,28 (m, 1H), 4,27 (m, 1H), 4,20 (m, 1H), 3,80 (d, J = 11,62 Hz, 1H), 3,73 (s, 3H), 3,29 (m, 1H), 1,86 (m, 1H), 1,50 (m, 1H), 1,37 (m, 1H), 1,30 (t, J = 7,47Hz, 3H), 0,90 (m, 1H), 0,71 (t, J = 7,4 Hz, 3H).

Ejemplo 453

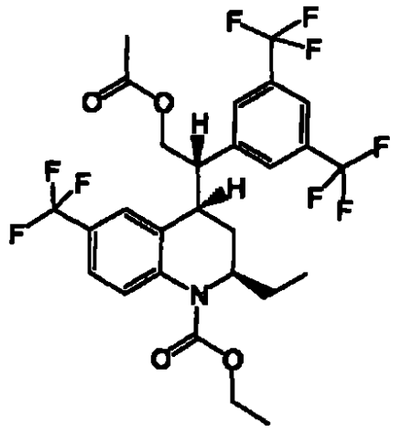


Éster etílico del ácido (*R, S)* y *(R, R)* 4-[2-acetoxi-1-(3,5-bis-trifluorometilfenil)etil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico

A una solución de la mezcla diastereoisomérica éster etílico del ácido (*R, R*) y (*R, S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico (Ejemplo 437, 57 mg, 0,102 mmol) en diclorometano (1 ml) en una atmósfera de nitrógeno se le añadió trietilamina (43 µl, 0,306 mmol) seguido de cloruro de acetilo (9 µl, 0,132 mmol). Después de 3 horas, la mezcla se repartió ente agua y diclorometano, la capa orgánica se separó, se secó sobre sulfato sódico anhidro y se evaporó al vacío. El residuo se purificó por cromatografía en gel de sílice eluyendo con hexanos y después con hexanos/acetato de etilo 19:1, después 9:1, después 4:1, después 3:7 y por último 2:3 para dar el compuesto del título en forma de una mezcla de diastereoisómeros (51 mg).

MS: 598,3 $[M+H]^+$ encontrado.

Ejemplo 454



Éster etílico del ácido (*R, R, S*) 4-[2-acetoxi-1-(3,5-bis-trifluorometil-fenil)- etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

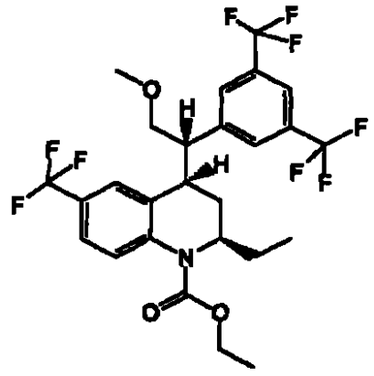
A una solución de éster etílico del ácido (*R, R, S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 447, 50 mg, 0,0896 mmol) en diclorometano (1 ml) en una atmósfera de nitrógeno se le añadió trietilamina (37 µl, 0,269 mol) seguido de cloruro de acetilo (8,3 µl, 0,116 mmol). Después de 30 minutos, la mezcla se repartió entre agua y diclorometano, la capa orgánica se separó, se secó sobre sulfato sódico acuoso y se evaporó al vacío. El residuo se purificó por cromatografía en gel de sílice eluyendo con hexanos, después con hexanos/acetato de etilo 19:1, después 9:1, después 4:1 para dar el compuesto del título (41 mg).

MS: 600,4 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,88 (s, 1H), 7,85 (s, 1H), 7,73 (s, 2H), 7,64 (m, 1H), 7,62 (m, 1H), 4,80 (dd, J = 11,62 Hz, 4,15 Hz, 1H), 4,29 (m, 1H), 4,25 (m, 1H), 4,23 (m, 1H), 4.20 (m, 1H), 3,72 (ddd, J = 9,13, 9,13, 3,32 Hz, 1H), 2,79 (m, 1H), 1,97 (s, 3H), 1,84 (m, 1H), 1,46 (m, 1H), 1,32 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0,87 (m, 1H), 0,69

(t, J = 7,47 Hz, 3H).

Ejemplo 455



Éster etílico del ácido (*R*, *R*, *S*) 4-[1-(3,5-bis-trifluorometil-fenil)-2-metoxi-2-etil]]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

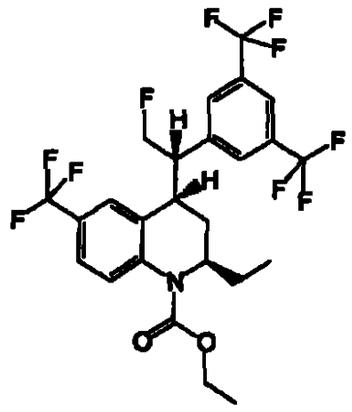
A una solución de éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 447, 20 mg, 0,035 mmol) en tetrahidrofurano (1 ml) en una atmósfera de nitrógeno se le añadió hidruro sódico (dispersión al 60% en aceite mineral, 0,043 mmol, 1,7 mg) seguido después de 5 minutos de yodometano (2 gotas). Después de agitar durante 16 horas se añadieron más alícuotas de hidruro sódico (2 mg) y yodometano (3 gotas). La mezcla se agitó a temperatura ambiente durante 48 horas y después se diluyó con acetato de etilo. La mezcla se lavó con agua, la capa orgánica se separó, se secó sobre sulfato sódico anhidro y se evaporó al vacío. El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con hexanos, después con hexanos/acetato de etilo 19:1, después 9:1 para dar el compuesto del título (19 mg).

MS: 572,5 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,81 (s, 1H), 7,76 (s, 2H), 7,61 (s a, 1H), 7,52 (m, 2H), 4,27 (m, 1H), 4,24 (m, 1H), 4,21 (m, 1H), 3,89 (dd, J = 9,96, 3,32 Hz, 1H), 3,74 (dd, J =

9,13, 7,47 Hz, 1H), 3,55 (m, 1H), 3,29 (s, 3H), 2,85 (m, 1H), 1,80 (m, 1H), 1,47 (m, 1H), 1,32 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0,87 (m, 1H), 0,69 (t, J = 7,47 Hz, 3H).

Ejemplo 456



Éster etílico del ácido (*R, R, S*) 4-[1-(3,5-bis-trifluorometil-fenil)-2-fluoro-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

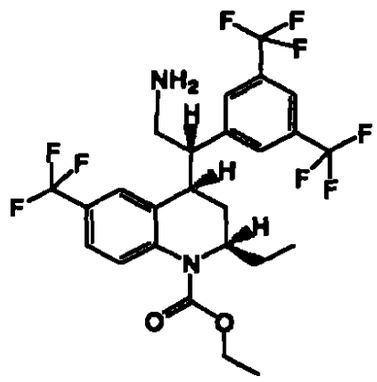
A una solución de éster etílico del ácido (*R, R, S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 447, 20 mg, 0,0035 mmol) en diclorometano (1 ml) en una atmósfera de nitrógeno se le añadió trifluoruro de dietilaminoazufre(47 µl, 0,358 mmol). La mezcla se agitó a temperatura ambiente durante 3 horas y después se añadió otro alícuota de trifluoruro de dietilaminoazufre (47 µl, 0,358 mmol). Después de 1 hora, la mezcla se repartió entre agua y diclorometano, la capa orgánica se separó, se secó sobre sulfato sódico acuoso y se evaporó al vacío. El residuo se purificó inicialmente por cromatografía en gel de sílice eluyendo con hexanos, después con hexanos/acetato de etilo 19:1, después 9:1 y se purificó finalmente por HPLC de fase inversa usando el sistema de HPLC preparativa de Shimadzu (Shimadzu Corporation, Kyoto, Japón) eluyendo con un gradiente de 30-100% acetonitrilo/agua/ácido fórmico al 0,1% en una

columna de 19x50 cm Waters Symmetry (Waters Corp., Milford, MA) 8 minutos, gradiente 6 minutos, 25 ml/min, recogida disparada por UV, observancia a 210 nm. Las fracciones que contenían el producto se evaporaron a sequedad para dar el compuesto del título (3 mg).

MS: 560,3 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,86 (s, 1H), 7,80 (s, 2H), 7,55 (m, 2H), 7,54 (s, 1H), 4,93 (ddd, J = 46,47, 9,96, 4,14 Hz, 1H), 4,82 (ddd, J = 46,47, 9,96, 6,64 Hz, 1H), 4,28 (m, 1H), 4,27 (m, 1H), 4,23 (m, 1h), 3,72 (m, 1H), 2,91 (m, 1H), 1,88 (m, 1H), 1,48 (m, 1H), 1,34 (m, 1H), 1,32 (t, J = 7,47 Hz, 3H), 0,92 (m, 1H), 0,71 (t, J = 7,47 Hz, 3H).

Ejemplo 457



Éster etílico del ácido (*R, R, S*) 4-[1-(3,5-bis-trifluorometil-fenil)-2-amino-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

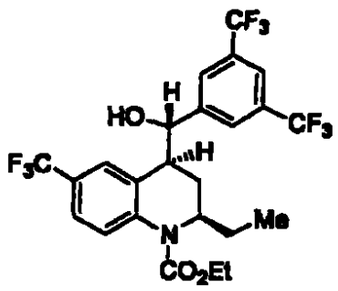
A una solución de éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico(Ejemplo 438, 25 mg, 0,0438 mmol) en tetrahidrofurano (3 ml) en una atmósfera de nitrógeno se le añadió un complejo de borano-dimetilsulfuro (8,3 µl, 0,0876 mmol). La mezcla se calentó a 70°C durante 48 horas y después se añadió agua (2,5 ml) y una solución saturada acuosa de carbonato sódico (1 ml). La mezcla se

calentó a 70°C durante 1 hora y después se repartió entre agua y diclorometano. La capa orgánica se evaporó a sequedad al vació y el residuo se disolvió en éter dietílico (5 ml) y se añadió ácido clorhídrico 2N (1 ml). Después de 24 horas, la mezcla se diluyó con agua, se añadió una solución de carbonato sódico y la mezcla se extrajo con diclorometano. La capa orgánica se secó sobre sulfato sódico anhidro y el disolvente se evaporó al vacío. El producto en bruto se purificó por cromatografía en gel de sílice eluyendo con hexanos, después con hexanos/acetato de etilo 3:1, después acetato de etilo para dar el compuesto del título (18,5 mg).

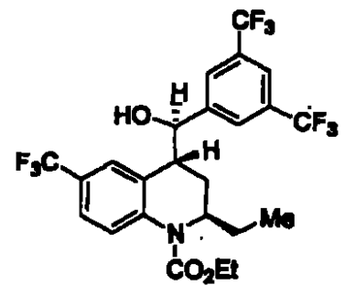
MS: 557,4 $[M+H]^+$ encontrado.

^{1}H RMN ($CDCl_3$) □ 7,84 (s, 1H), 7,77 (s, 2H9, 7,58 (s a, 1H), 7,52 (m, 2H), 4,27 (m, 1H), 4,23 (m, 1H), 4,22 (m, 1H), 3,44 (dd, J = 13,28, 3,32 Hz, 1H), 3,35 (m, 1H), 3,09 (dd, J = 13,28, 9,13 Hz, 1H), 2,76 (m, 1H), 1,76 (m, 1H), 1,45 (m, 1H), 1,34 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0,84 (m, 1H), 0,69 (t, J = 7,47 Hz, 3H).

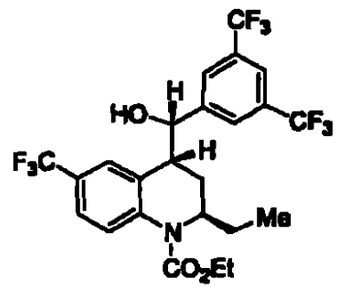
Ejemplos 458, 459, 460 y 461



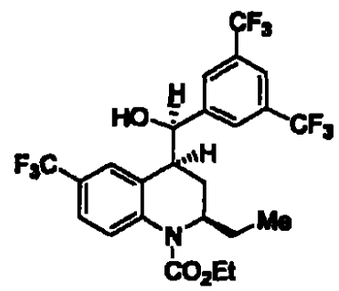
Éster etílico del ácido [(*R, S, S*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido [(*R*, *R*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido [(*R*, *R*, *S*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

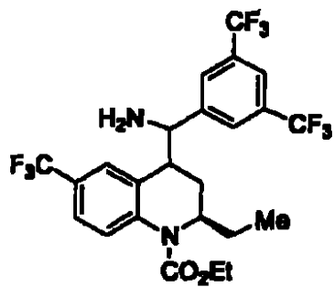


Éster etílico del ácido [(*R*, *S*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Estos compuestos, preparados previamente en los Ejemplos 22, 23, 24 y 25 se prepararon en forma enriquecida ópticamente por resolución del racemato indicado

correspondiente, o de un intermedio en su síntesis, usando procedimientos análogos a aquellos descritos en este documento.

Ejemplos 462, 463, 464 y 465



Preparación del éster etílico del ácido [(*R*, *R*, *R*)], [(*R*, *R*, *S*)], [(*R*, *S*, *R*)] y [(*R*, *S*, *S*)]-4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Procedimiento general para preparar compuestos amina: se introdujo éster etílico del ácido [(*R*, *R*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,527 gramos, 0,971 mmol, 1 eq) en un matraz de fondo redondo equipado con una barra de agitación magnética. Se añadió cloruro de metileno (20 ml) seguido de la adición de trietilamina (0,456 ml, 3,37 mmol, 3,37 eq) y cloruro de mesilo (0,150 ml, 1,94 mmol, 2,0 eq) a temperatura ambiente y la mezcla de reacción se agitó durante una noche. La mezcla de reacción se inactivó con agua, se extrajo 4 veces con acetato de etilo. La capa orgánica se lavó con HCl 0,1M, seguido de solución saturada de bicarbonato y se secó sobre sulfato sódico. La solución se filtró, se concentró y se secó al vacío para proporcionar éster etílico del ácido [(*R*, *R*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-metanosulfoniloxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,599 gramos, rendimiento 99%) en forma de sólido blanco, MS (ES+) m/z = 622 (M+1).

El éster etílico del ácido [(*R*, *R*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-

metanosulfoniloxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,313 gramos, 0,504 mmol, 1 eq) se introdujo en un matraz de fondo redondo equipado con una barra de agitación magnética. Se añadió DMF (12 ml) seguido de la adición de azida sódica (0,201 gramos, 0,3010 mmol, 6,1 eq). La mezcla de reacción se calentó a 70°C durante 12 horas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó en 200 ml de EtOAc y se lavó 4 veces con salmuera y agua. El EtOAc se recogió, se secó sobre sulfato sódico, se filtró y se concentró. El material se purificó en un Biotage Flash 40s para proporcionar éster etílico del ácido [(*R*, *R*, *S*)]-4-[azido-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,202 gramos, rendimiento 71%) MS (ES+) m/z = 569 (M+1).

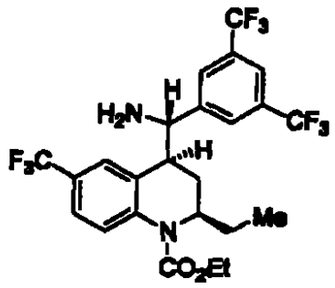
El éster etílico del ácido [(*R*, *R*, *S*)]-4-[azido-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,202 g, 0,356 mol, 1 eq) se introdujo en un matraz de fondo redondo y equipado con una barra de agitación magnética y un condensador de reflujo. Se añadió NH_4CO_2H (0,226 gramos, 3,58 mmol, 10,1 eq) y Pd/C (0,113 gramos, 0,107 mol, 0,30 eq) seguido de la adición de una solución 2:1 de metanol y acetato de etilo (8,80 ml). La mezcla de reacción se calentó a reflujo durante 2 horas y después se filtró a través de Celite®. El filtrado se concentró, aunque no a sequedad, y se repartió entre acetato de etilo y solución acuosa de bicarbonato sódico. La capa orgánica se recogió, se secó sobre sulfato sódico, se filtró y se concentró. El material en bruto se purificó en Biotage Flash 40 M para proporcionar el compuesto deseado, éster etílico del ácido [(*R*, *R*, *S*)]-4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,162 gramos, rendimiento 83%) MS (ES+) m/x = 543 (M+1).

^{1}H RMN ($CDCl_3$): □ 0,82 (t, 3H), 1,32 (t, 3H), 1,34-1,57 (m, 3H), 2,53 (m, 1H), 3,00 (m, 1H), 4,28 (q, 2H), 4,50 (m, 1H), 7,03 (s, 1H), 7,42 (d, 1H), 7,60 (d, 1H), 7,66

(s, 2H), 7,72 (s, 1H).

MS (ES+) m/z = 543 (M+1)

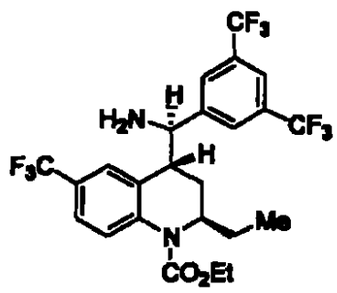
Estos compuestos adicionales se prepararon usando procedimientos análogos a los descritos en este documento:



Éster etílico del ácido [(*R, S, S*)]-4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 0,71 (t, 3H), 1,00 (m, 1H), 1,29 (t, 3H), 1,33-1,52 (m, 2H), 1,67 (m, 1H & H_2O), 2,70 (m, 1H), 4,15-4,31 (m, 3H), 4,47 (d, 1H), 7,51 (m, 2H), 7,84 (s, 1H), 7,89 (s, 2H), 7,91 (s, 1H).

MS (ES+) m/z = 543 (M+1)

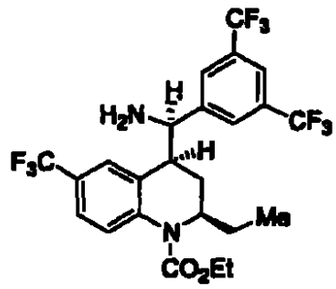


Éster etílico del ácido [(*R, R, R*)]-4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 0,75 (t, 3H), 1,33 (t, 3H), 1,37-1,62 (m, 3H), 1,82 (m, 1H), 2,98 (m, 1H), 4,17-4,36 (m, 4H), 7,51 (s, 1H), 7,53-7,61 (m, 2H), 7,83 (s, 1H), 7,86 (s,

2H).

MS (ES+) m/z = 543 (M+1)



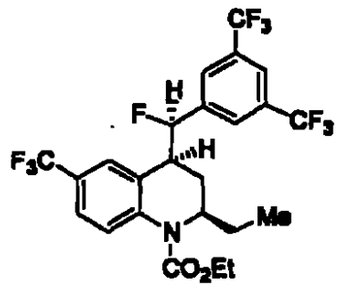
Éster etílico del ácido [(*R, S, R*)]-4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-etil-6-2-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 0,82 (t, 3H), 1,27 (t, 3H), 1,40-1,64 (m, 3H), 2,07 (m, 1H), 2,76 (m, xH), 4,09-4,27 (m, 3H), 5,07 (m, 1H), 7,55 (q, 2H), 7,66 (s, 1H), 7,83 (s, 1H), 7,96 (s, 2H);

MS (ES+) m/z = 543 (M+1)

Ejemplos 466, 467, 468 y 469

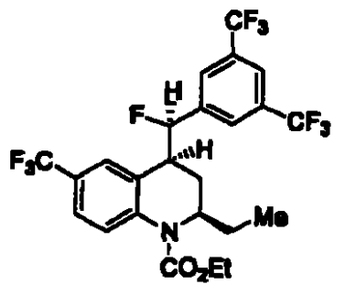
Los siguientes compuestos se prepararon con materiales de partida y procedimientos análogos a los descritos anteriormente, particularmente en los Ejemplos 18, 19 y 456.



Éster etílico del ácido [(*R, S, R*)]-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 7,92 (s, 1H), 7,83 (s, 2H), 7,67 (s, 1h), 7,57 (s, 2H), 6,5 (d, 1H), 4,24 (m, 3H), 2,91 (dd, 1h), 2,08 (m, 1H), 1,51 (m, 3H), 1,27 (t, 3H), 0,80 (t, 3H);

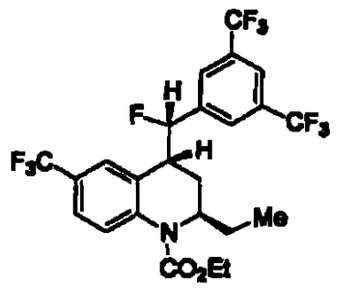
MS (ES+) m/z = 546,3 $[M+H]^+$ encontrado.



Éster etílico del ácido [(*R, S, S*)]-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 7,96 (s, 1H), 7,88 (s, 2H), 7,76 (s, 1H), 755 (s, t, 2H), 5,86 (dd, J = 9,13 Hz,1H), 4,25 (m, 3H), 3,10 (m, 1H), 1,75 (m, 1H), 1,47 (m, 2H), 1,29 (t, 3H), 1,18 (t, 3H), 0,77 (t, 3H);

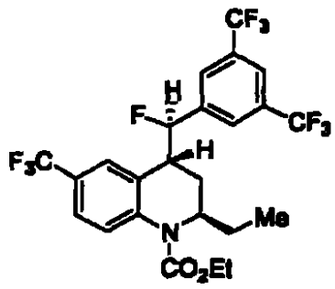
MS (ES+) m/z = 546,4 $[M+H]^+$ encontrado.



Éster etílico del ácido [(*R, R, S*)]-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 7,8 (s, 1H), 7,59 (d, 1H), 7,47 (d, 1H), 7,43 (s, 3H), 6,86 (s, 1H), 5,65 (dd, J = 7,88 Hz, 1H), 4,60 (m, 1H), 4,28 (m, 2H), 3,21 (m, 1H), 2,65 (m, 3H), 1,74 (m, 1H), 1,41-1,62 (m, 2H), 1,31 (t, 3H), 0,86 (t, 3H).

MS (ES+) m/z = 546,3 $[M+H]^+$ encontrado.



Éster etílico del ácido [(*R, R, R*)]-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 7,88 (s, 1H), 7,63 (s, d, 3H), 7,52 (d, 1H), 7,41 (s, 1H), 5,58 (dd, J = 7,47 Hz, 1H), 4,42 (m, 1H), 4,24 (m, 2H), 3,40 (m, 1H), 1,97 (m, 1H), 1,74 (m, 1H) ,1,41 (m, 2H), 1,27 (t, 3H), 0,79 (t, 3H).

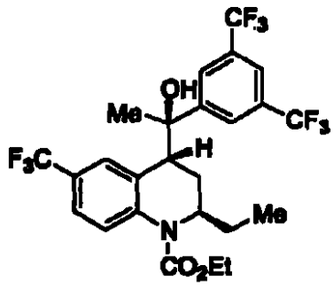
MS (ES+) m/z = 546,3 $[M+H]^+$ encontrado.

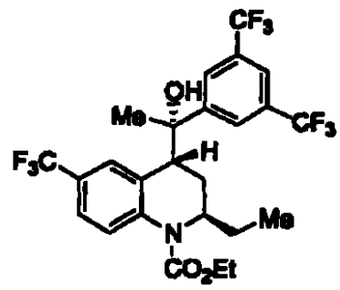
Ejemplos 470, 471, 472 y 473

Los siguientes compuestos se prepararon con materiales de partida y procedimientos análogos a los descritos anteriormente, como se muestra en el Esquema 2 en los que la adición de un derivado organometálico adecuado tal como un derivado de magnesio o litio, preparado con un compuesto alquil-Hal, donde Hal representa un átomo de cloro, bromo o yodo, a XXV produjo los compuestos mostrados en los Ejemplos 470, 471, 472 y 473.

Se introdujo éster etílico del ácido [(*R, R*), (*S, S*)]-4-[(3,5-bis-trifluorometil-benzoil)]-6-trifluorometil-2-etil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,015 gramos en un pequeño matraz de fondo redondo que contenía una barra de agitación magnética y se disolvió en 0,50 ml de tetrahidrofurano : Se añadió una solución de bromuro de metil magnesio (0,028 mmol de 3,0M en éter dietílico) a la mezcla de reacción a temperatura ambiente y se agitó durante 2 horas. Después, la mezcla de reacción se

inactivó con una solución saturada de cloruro de amonio y se extrajo en acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar los productos deseados en forma de aceite en bruto. Los diastereoisómeros del alcohol se separaron por cromatografía en gel de sílice para proporcionar éster etílico del ácido [(*R*, *R*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)]-1-hidroxil-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico y éster etílico del ácido [(*R*, *R*, *S*)]-4-[(3,5-bis-trifluorometil-fenil)]-1-hidroxil-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico.





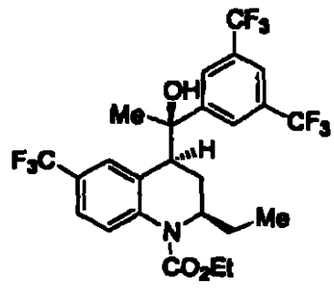
Éster etílico del ácido [(*R*, *R*, *R*), (*R*, *R*, *S*)]-4-[(3,5-bis-trifluorometil-fenil)]-1-hidroxil-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

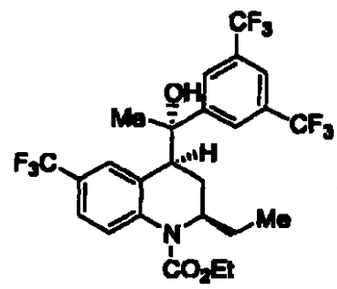
Compuesto que eluye en primer lugar: ^{1}H RMN ($CDCl_3$): □ 7,86 (s, 2H), 7,80 (s, 1H), 7,53 (d, 1H), 7,42 (d, 1H), 7,06 (s, 1H), 4,41 (m, 1H), 4,2 (q, 2H), 3,18 (m, 1H), 2,30 (m, 1H), 1,91 (s a, 1H), 1,62-1,74 (m, 4H), 1,24-1,43 (m, 5H), 0,77 (t, 3H).

MS: 588,3 $[M+H]^+$ encontrado.

Compuesto que eluye en segundo lugar: ^{1}H RMN ($CDCl_3$): □ 7,76 (m, 3H), 7,53 (d, 1H), 7,42 (d, 1H), 7,06 (s, 1H), 4,41 (m, 1H), 4,2 (q, 2H), 3,18 (m, 1H), 2,30 (m, 1H), 1,91 (s a, 1H), 1,62-1,74 (m, 4H), 1,24-1,43 (m, 5H), 0,77 (t, 3H).

MS: 588,3 $[M+H]^+$ encontrado.





Éster etílico del ácido [(*R, S, R*), (*R, S, S*)]-4-[(3,5-bis-trifluorometil-fenil)]-1-hidroxil-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Compuesto que eluye en primer lugar: ^{1}H RMN ($CDCl_3$): □ 7,86 (s, 2H), 7,80 (s, 1H), 7,70 (d, 1H), 7,55 (m, 2H9, 7,35 (s, 1H), 4,3 (m, 2H), 4,19 (m, 1H), 3,20 (m, 1H), 1,91 (m, 1H), 1,60 (s, 3H), 1,30 (t, 3H), 0,70 (t, 3H).

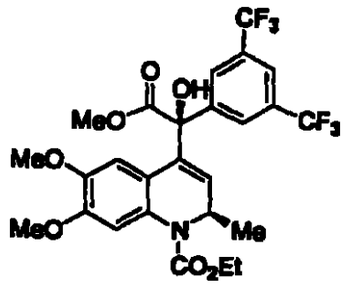
MS: 556,2 $[M-H]^-$ encontrado.

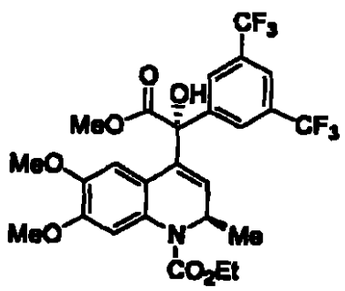
Compuesto que eluye en segundo lugar: ^{1}H RMN ($CDCl_3$): □ 8,0 (s, 2H), 7,80 (s, 1H), 7,50 (s a, 1H), 7,40 (dd, 2H), 4,4 (m a, 1H), 4,20 (m, 2H), 3,05 (d, 1H), 2,55 (m a, 1H), 1,74 (s, 3H), 1,63 (m, 1H), 1,43 (m, 2H), 1,30 (t, 3H), 0,90 (t, 3H)

MS: 558,3 $[M+H]^+$ encontrado.

Ejemplos 474 y 475

Los siguientes compuestos se prepararon con materiales de partida y procedimientos análogos a los descritos anteriormente en el Esquema 1, particularmente en el Ejemplo 2.





Éster etílico del ácido [(*R*, *R*), (*R*, *S*)]-4-[(3,5-bis-trifluorometil-fenil)]-1-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-2*H*-quinolin-1-carboxílico

Diastereómero 1: ^{1}H RMN ($CDCl_3$): □ 7,92 (s, 2H), 7,73 (s, 1H), 6,81 (s, 1H), 5,80 (d, 1H), 5,20 (m a, 1H), 4,40 (s a, 1H), 4,30 (m, 1H), 4,20 (m a, 1H), 3,84 (s, 3H), 3,80 (s, 3H), 3,50 (s, 3H), 1,34 (m, 4H), 1,09 (d, 3H);

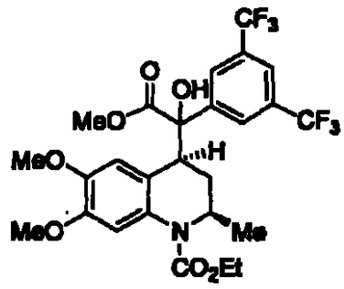
MS: 578,5 $[M+H]^+$ encontrado.

Diastereómero 2: ^{1}H RMN ($CDCl_3$): □ 8,18 (s, 2H), 7,87 (s, 1H), 6,67 (s, 1H), 5,65 (s a, 1H), 5,15 (s a, 1H), 4,31 (m a, 1H), 4,20 (m a, 1H), 3,86 (s, 3H), 3,80 (s, 3H), 3,58 (s, 3H), 1,33 (t, 3H), 1,09 (d, 3H).

MS: 578,6 $[M+H]^+$ encontrado.

Ejemplos 476 y 477

Los siguientes compuestos se prepararon con materiales de partida y procedimientos análogos a los descritos anteriormente en el Esquema 1, particularmente en los Ejemplos 7 y 8.



Éster etílico del ácido [(*R, S, R*), (*R, S, S*)]-4-[(3,5-bis-trifluorometil-fenil)]-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Compuesto que eluye en primer lugar: ^{1}H RMN ($CDCl_3$): □ 8,18 (s, 2H), 7,03 (s a, 1h), 6,73 (s, 1H), 4,31 (m, 1H), 4,20 (m, 2H), 3,88 (s, 3H), 3,86 (s, 3H), 3,81 (s, 3H), 3,30 (d, 1H), 1,70 (m, 2H), 1,21-1,30 (t, m, 4H), 1,09 (d, 3H);

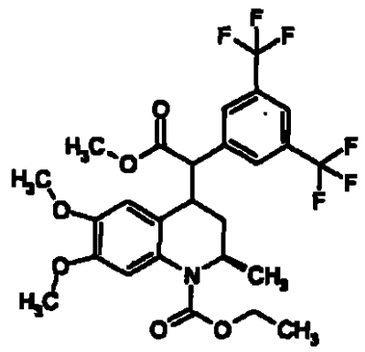
MS: 580,6 $[M+H]^+$ encontrado.

Compuesto que eluye en segundo lugar: ^{1}H RMN ($CDCl_3$): □ 8,25 (s, 2H), 7,84 (s, 1H), 6,92 8br s, 1H), 6,30 (s, 1H), 4,55 (m, 1H), 4,30 (m, 1H), 4,20 (m, 1H), 3,88 (s, 3H), 3,80 (s, 3H), 3,60 (d, 1H), 3,40 (s, 3H), 2,03 (m, 2H), 1,55 (m, 1H), 1,32 (t, 3H), 1,09 (d, 3H);

MS: 580,5 $[M+H]^+$ encontrado.

Ejemplos 478 y 479

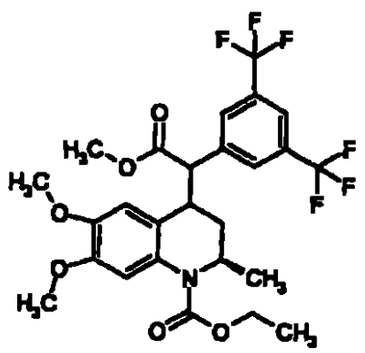
Los siguientes compuestos se prepararon con materiales de partida y procedimientos análogos a los descritos anteriormente, particularmente en los Ejemplos 448, 449, 450 y 451.



Éster etílico del ácido [(*R*, *R*, *R*), (*R*, *R*, *S*)]-4-[(3,5-bis-trifluorometil-fenil)]-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 7,97 (s, 2H), 7,83 (s, 1H), 7,0 (s a, 1H), 6,20 (s, 1H), 4,50 (m, 1H), 4,30 (m, 1H), 4,30 (m, 1H), 4,19 (m, 1H), 4,17 (d, 1H), 3,80 (s, 3H), 3,74 (s, 3H), 3,51 (s, 3H), 3,32 (m, 1H), 2,30 (m, 1H), 1,31 (t, 3H), 1,20 (d, 3H);

MS: 564,5 $[M+H]^+$ encontrado.



^{1}H RMN ($CDCl_3$): □ 7,87 (s, 3H), 7,03 (s a, 1H), 6,72 (s, 1H), 4,31 (m, 2H), 4,20 (m, 1H), 3,98 (d, 1H), 3,86 (s, 6H), 3,75 (s, 3H), 3,32 (t, 1H), 1,70 (m, 1H), 1,30 (t, 3H), 1,07 (d, 3H), 0,80 (m, 1H);

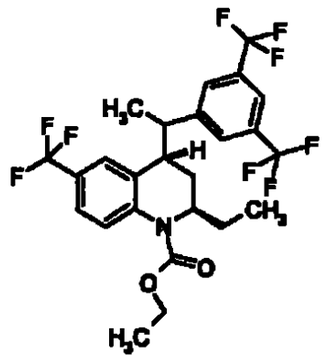
MS: 564,4 $[M+H]^+$ encontrado.

Ejemplos 480

Los siguientes compuestos se prepararon con materiales de partida y procedimientos análogos a los descritos anteriormente, particularmente en los Ejemplos 470, 471, 472 y 473.

Se introdujo éster etílico del ácido [(*R*, *R*, *R*), (*R*, *R*, *S*)]-4-[(3,5-bis-trifluorometil-fenil)]-1-hidroxil-etil]-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,079 g, 0,142 mmol) en un pequeño matraz de fondo redondo que contenía una barra de agitación magnética y se disolvió en 1,5 ml de cloroformo anhidro. A esta solución de reacción se le añadió 2,6-di-t-butil-4-metilpiridina (0,117 g, 0,568 mmol) y cloruro de tionilo (0,051 g, 0,425 mmol) y se dejó agitar a temperatura ambiente durante cuatro horas. La mezcla de reacción se inactivó con agua y se extrajo en cloruro de metileno. Las capas orgánicas se lavaron con HCl 0,1N, se secaron sobre sulfato de magnesio, se filtraron y se concentraron para proporcionar éster etílico del ácido [(*R*, *R*, *R*)], [(*R*, *R*, *S*)]-4-[1-(3,5-bis-trifluorometil-fenil)]-1-cloro-etil]]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico en forma de un aceite que se usó sin purificación adicional. El éster etílico del ácido [(*R*, *R*, *R*)], [(*R*, *R*, *S*)]-4-[1-(3,5-bis-trifluorometil-fenil)]-1-cloro-etil]]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico en forma de un aceite que se usó sin purificación adicional (0,085 g, 0,142 mmol) se introdujo en un pequeño matraz de fondo redondo que contenía una barra de agitación magnética y se disolvió en 0,48 ml de THF. A esta solución se le añadió ácido acético glacial (0,48 mmol), HCl (0,80 mmol) y polvo de cinc (0,093 g, 1,42 mmol). La mezcla de reacción se agitó a temperatura ambiente durante tres horas. La mezcla de reacción se inactivó con agua y se extrajo tres veces con acetato de etilo. La capa orgánica se lavó con agua, se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar éster etílico del ácido [(*R*, *R*]-4-[1-(3,5-bis-trifluorometil-fenil)-vinil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico en forma de un aceite.

El éster etílico del ácido [(*R*, *R*]-4-[1-(3,5-bis-trifluorometil-fenil)-vinil]- 2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico en forma de un aceite (15 mg) se introdujo en un pequeño matraz de fondo redondo y se disolvió en 10 ml de metanol. A esta solución se le añadieron 10 mg de Pd/C al 10%. La mezcla de reacción se hidrogenó a 45 psi durante 12 horas. Después, la mezcla de reacción se filtró a través de Celite® y se lavó con metanol. El filtrado se concentró hasta un aceite y se purificó por cromatografía en gel de sílice para proporcionar éster etílico del ácido [(*R*, *R*, *R*)], [(*R*, *R*, *S*)]-4-[1-(3,5-bis-trifluorometil-fenil)-etil]-6,7-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico con un rendimiento del 66%.

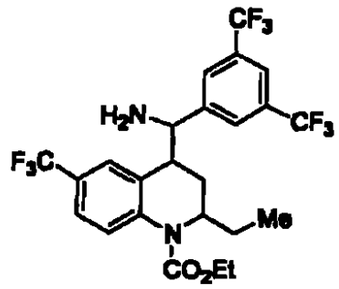


Éster etílico del ácido [(*R*, *S*, *R*)], [(*R*, *S*, *S*)]-4-[1-(3,5-bis-trifluorometil-fenil)-etil]-2-etil-6,7-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

^{1}H RMN ($CDCl_3$): □ 7,78 (s, 1H), 7,65 (s, 2H), 7,59 (dd, 2H), 7,41 (s, 1H), 4,30 (m, 1H), 4,20 (m, 2H), 2,95 (m, 2H), 1,80 (m, 1H), 1,58 (m, 2H), 1,40 (m, 1H), 1,30 (t, 3H), 1,20 (d, 3H), 0,72 (t, 3H).

MS: 542,3 $[M+H]^+$ encontrado.

Ejemplo 481 (Estereoisómeros de los Ejemplos 462, 463, 464 y 465)



Éster etílico del ácido [(*S, R, S*)], 4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido [(*S, S, S*)], 4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

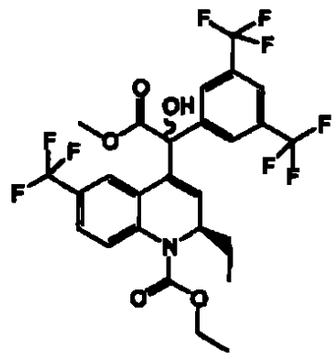
Éster etílico del ácido [(*S, R, R*)], 4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido [(*S, S, R*)], 4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto.

Los estereoisómeros anteriores de los ejemplos 462, 463, 464 y 465 son proféticos y pueden prepararse en forma enriquecida ópticamente por resolución del racemato correspondiente indicado, o de un intermedio en su síntesis, usando procedimientos análogos a los descritos en este documento.

Ejemplos 482 y 483



Éster etílico del ácido (*R*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)]-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2*H*-quinolin-1-carboxílico;

La mezcla de los dos diastereoisómeros (Ejemplo 2, 1,0 g) se cromatografió en sílice (columna Flash 40M, Biotage, Dyar Corp., Charlottesville, VA) eluyendo con un gradiente de cloruro de metileno-hexanos de 2:3 a 4:1 para dar los compuestos del título en forma de sólidos blancos.

Diastereoisómero que eluye en primer lugar (estereoquímica 4a no determinada):

MS: 597,9 $[M-H]^-$ encontrado

^{1}H RMN ($CDCl_3$): □ 7,92 (s, 1H), 7,65 (d, J = 8,30 Hz, 1H), 7,34 (dd, J = 8,30, 1,66 Hz, 1H), 5,97 (d, J = 6,64 Hz, 1H), 5,04 (m, 1H),4,53 (s, 1H), 4,27 (m, 2H), 3,87 (s, 3H), 1,47 (m, 1H), 1,35 (m, 1H), 1,28 (t, J = 7,47 Hz, 3H), 0,85 (d, J = 6,64 Hz, 3H).

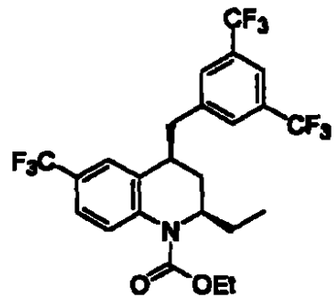
Diastereoisómero que eluye en segundo lugar (estereoquímica 4a no determinada):

MS: 597,9 $[M-H]^-$ encontrado

^{1}H RMN ($CDCl_3$): □ 8,16 (s, 2H), 7,90 (s, 1H), 7,65 (d, J = 8,30 1H), 7,63 (s, 1H), 7,45 (dd, J = 8,30, 1,66 Hz, 1H), 5,82 (d, J = 6,42 Hz, 1H), 4,96 (m, 1H), 4,34 (s, 1H), 4,27 (m, 2H), 3,78 (s, 3H), 1,47 (m, 1H), 1,35 (m, 1H), 1,33 (t, J = 7,47 Hz, 3H),

0,83 (d, J = 7,48 Hz, 3H).

Ejemplo 484



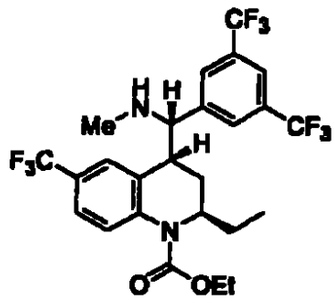
Éster etílico del ácido (*R*, *R*)]-4-[(3,5-bis-trifluorometil-bencil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se introdujo éster etílico del ácido [(*R*, *R*, *R*)]-4-[(3,5-bis-trifluorometil-fenil)-metanosulfoniloxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,045 mmol, 0,0278 g) en un matraz de reacción de 5ml. A esto se le añadieron 1,3 ml de DMF seguido de borohidruro sódico (0,526 mmol, 0,019 g). La reacción se calentó a 85°C durante 12 horas. Después, la mezcla de reacción se diluyó con acetato de etilo y se lavó con una solución acuosa de salmuera. La capa orgánica se recogió, se secó sobre sulfato sódico, se filtró y se concentró a sequedad. La mezcla de reacción en bruto se purificó por cromatografía en gel de sílice para proporcionar 18,5 mg del producto deseado éster etílico del ácido (*R*, *R*)-4-(3,5-bis-trifluorometil-bencil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico con un rendimiento del 78%.

^{1}H RMN ($CDCl_3$): 0,80 ppm (t, 3H), 1,10 (m,1 H), 1,29 (t, 3H), 1,41-1,62 (m, 2H & H_2O), 2,16 (m, 1H), 2,76-2,,87 (m, 2H), 3,64 (d, 1H), 4,15-4,32 (m, 3H), 7,47 (s, 1H), 7,51-7,57 (m, 2H), 7,70 (s, 2H), 7,80 (s, 1H).

MS (ES+) m/z = 528 (M+1)

Ejemplo 485



Éster etílico del ácido (*R*, *R*, *S*) 4-[(3,5-bis-trifluorometil-fenil)-metilaminometil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se introdujo éster etílico del ácido (*R*, *R*, *S*)] 4-[amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,193 g, 0,357 mmol) en un tubo cerrado herméticamente que contenía 7 ml de formiato de etilo. El tubo se cerró herméticamente y se calentó durante 12 horas a 100ºC. Después, la mezcla de reacción se concentró y purificó por cromatografía en gel de sílice para proporcionar 0,165 g de formamida con un rendimiento del 81%. Después, este producto se introdujo en un matraz de fondo redondo equipado con una barra de agitación magnética y se disolvió en 7,3 ml de tolueno. A esta solución se le añadieron 2,92 ml de un complejo borano sulfuro de metilo en tolueno (2,0 M). Se acopló un condensador de reflujo al matraz y la reacción se calentó a 74ºC durante 12 horas. Después, la mezcla de reacción se inactivó con metanol y unas gotas de HCl. Después, esta mezcla se calentó durante 1 hora. Después de enfriar a temperatura ambiente, la mezcla se inactivó con $NaHCO_3$ acuoso y se extrajo 3 veces con acetato de etilo. Los materiales orgánicos se recogieron, se secaron sobre sulfato sódico y se concentraron a sequedad. El aceite en bruto se purificó por cromatografía en gel de sílice para proporcionar el éster etílico del ácido (*R*, *R*, *S*) 4-[(3,5-bis-trifluorometil-fenil)-

metilaminometil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico con un rendimiento del 41%.

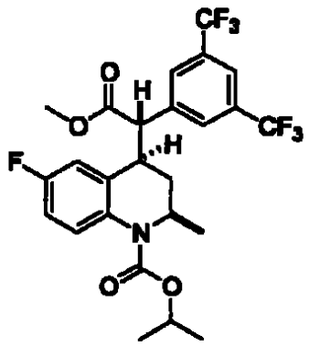
^{1}H RMN ($CDCl_3$): 0,81 ppm (t, 3H), 1,33 (t, 3H), 1,36-1,52 (m, 3H), 2,25 (s, 3H), 2,52 (m, 1H), 2,97 (m, 1H), 3,99 (d, 1H), 4,28 (m, 2H), 4,52 (m, 1H), 7,04 (s, 1H), 7,41 (m, 1H), 7,59-7,61 (m, 3H), 7,72 (s, 1H).

MS (ES+) m/z = 557 (M+1).

Ejemplos 486 - 499

Estos compuestos se prepararon con materiales de partida apropiados y con procedimientos análogos a los descritos en los Ejemplos 9, 10, 433, 434, 438, 443, 444, 452, 454, 457 y descritos generalmente en el Esquema 2. Los intermedios de bromo apropiadamente sustituidos designados como Fórmula XVII en el Esquema 2 se prepararon usando los procedimientos descritos por Matsugi en *Tetrahedron Lett* **2000**, *41*, 8523 y Hardy en la Patente de Estados Unidos Nº 6.288.075.

Ejemplo 486



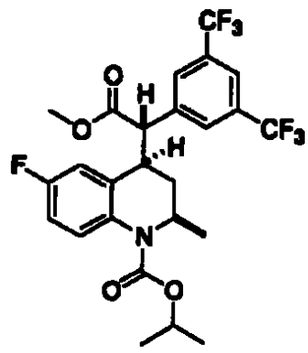
Éster isopropílico del ácido (*RS, RS, SR*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-6-fluoro-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

GCMS (EI): 535 (M+)

^{1}H RMN ($CDCl_3$): □ 0,87 (m, 1H), 1,04 (d, 3H), 1,25 (m, 3H), 1,32 (d, 3H), 1,69 (m, 1H), 3,33 (m, 1H), 3,76 (s, 3H), 3,92 (d, 1H), 4,29 (m, 1H), 5,03 (m, 1H), 6,81

(dd, 1H), 6,87 (m, 1H), 7,38 (s a, 1H), 7,85 (s, 2H), 7,87 (s, 1H).

Ejemplo 487

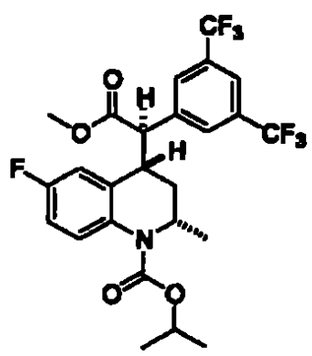


Éster isopropílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-6-fluoro-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

GCMS (EI): 535 (M+)

^{1}H RMN ($CDCl_3$): □ 0,83 (m, 1H), 1,04 (d, 3H), 1,26 (d, 3H), 1,32 (d, 3H), 1,72 (m, 1H), 3,33 (m, 1H), 3,77 (s, 3H), 3,91 (d, 1H), 4,28 (m, 1H), 5,03 (m, 1H), 6,82 (dd, 1H), 6,95 (m, 1H), 7,38 (s a, 1H), 7,84 (s, 2H), 7,87 (s, 1H).

Ejemplo 488

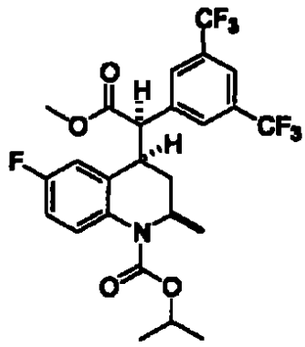


Éster isopropílico del ácido (S, *S, P*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-6-fluoro-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

GCMS (EI): 535 (M+)

^{1}H RMN ($CDCl_3$): □ 0,83 (m, 1H), 1,04 (d, 3H), 1,26 (d, 3H), 1,32 (d, 3H), 1,69 (m, 1H), 3,33 (m, 1H), 3,77 (s, 3H), 3,91 (d, 1H), 4,28 (m, 1H), 5,03 (m, 1H), 6,82 (dd, 1H), 6,95 (m, 1H), 7,38 (s a 1H), 7,84 (s, 2H), 7,87 (s, 1H).

Ejemplo 489

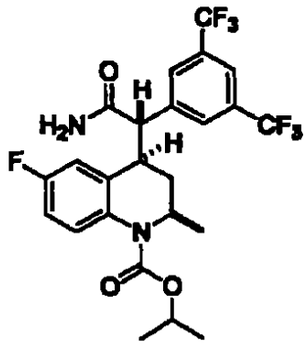


Éster isopropílico del ácido (*RS, RS, RS*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-6-fluoro-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

GCMS (EI): 535 (M+)

^{1}H RMN ($CDCl_3$): □ 0,87 (m, 1H), 1,17 (d, 3H), 1,26 (m, 3H), 1,32 (d, 3H), 2,31 (m, 1H), 3,28 (m, 1H), 3,74 (s, 3H), 4,17 (d, 1H), 4,46 (m, 1H), 5,04 (m, 1H), 6,44 (dd, 1H), 6,87 (m, 1H), 7,38 (m, 1H), 7,84 (s, 1H), 7,89 (s, 2H).

Ejemplo 490



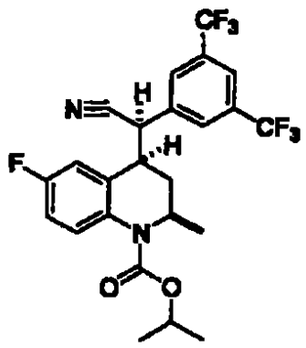
Éster isopropílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-

6-fluoro-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

GCMS (EI): 520 (M+)

^{1}H RMN ($CDCl_3$): □ 0,85 (m, 1H), 1,05 (d, 3H), 1,25 (m, 3H), 1,30 (d, 3H), 1,64 (m, 1H), 3,38 (m, 1H), 3,71 (d, 1H), 4,26 (m, 1H), 5,01 (m, 1H), 5,53 (s a 1H), 5,78 (s a, 1H), 6,93 (m, 2H), 7,37 (b, 1H), 7,85 (s, 2H), 7,87 (s, 1H).

Ejemplo 491

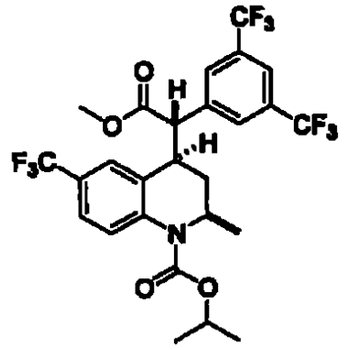


Éster isopropílico del ácido (*RS, RS, RS*) 4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-6-fluoro-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 503 (MH+)

^{1}H RMN ($CDCl_3$): □ 1,19 (d, 3H), 1,25 (d, 3H), 1,28 (d, 3H), 1,45 (m, 1H), 2,18 (m, 1H), 2,87 (m, 1H), 4,31 (m, 1H), 4,77 (d, 1H), 4,99 (m, 1H), 7,04 (s a, 1H), 7,06 (s a, 1H), 7,45 (m, 1H), 7,90 (s, 2H), 7,96 (s, 1H).

Ejemplo 492

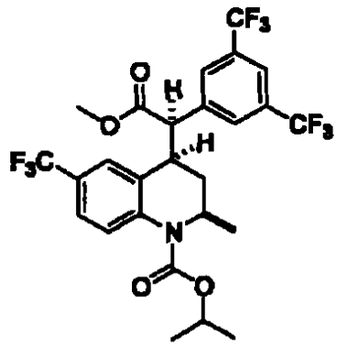


Éster isopropílico del ácido (*RS, RS, SR*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

GCMS (EI): 585 (M+)

^{1}H RMN ($CDCl_3$): □ 0,91 (m, 1H), 1,09 (d, 3H), 1,29 (d, 3H), 1,34 (d, 3H), 1,75 (m, 1H), 3,38 (t, 1H), 3,77 (s, 3H), 4,02 (d, 1H), 4,31 (m, 1H), 5,06 (m, 1H), 7,38 (s, 1H), 7,55 (m, 2H), 7,88 (s a, 3H).

Ejemplo 493



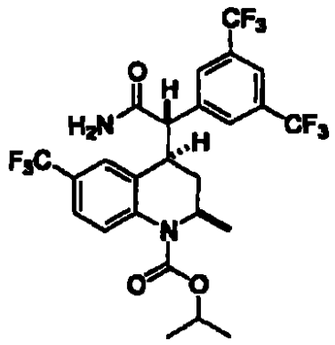
Éster isopropílico del ácido (*RS, RS, RS*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 585 (MH+)

^{1}H RMN ($CDCl_3$): □ 1,22 (d, 3H), 1,28 (d, 3H), 1,33 (d, 3H), 1,39 (m, 1H), 2,36

(m, 1H), 3,27 (m, 1H), 3,76 (s, 3H), 4,27 (d, 1H), 4,46 (m, 1H), 5,06 (m, 1H), 7,08 (m, 1H), 7,43 (d, 1H), 7,57 (d, 1H), 7,85 (s, 1H), 7,93 (s, 2H).

Ejemplo 494

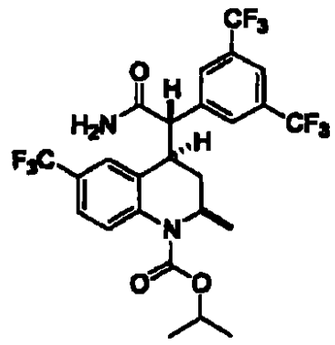


Éster isopropílico del ácido (*RS, RS, SR*) 4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 571 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,91 (m, 1H), 1,09 (d, 3H), 1,27 (d, 3H), 1,33 (d, 3H), 1,68 (m, 1H), 3,46 (t, 1H), 3,81 (d, 1H), 4,28 (m, 1H), 5,04 (m, 1H), 5,54 (s a, 1H), 5,82 (s a, 1H), 7,46 (s, 1H), 7,50 (d, 1H), 7,56 (d, 1H), 7,88 (s, 3H).

Ejemplo 495

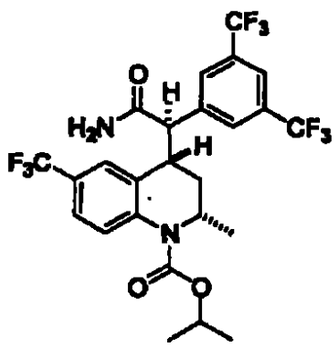


Éster isopropílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 571 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,87 (m, 1H), 1,09 (d, 3H), 1,26 (d, 3H), 1,33 (d, 3H), 1,69 (m, 1H), 3,45 (t, 1H), 3,83 (d, 1H), 4,27 (m, 1H), 5,03 (m, 1H), 5,65 (s a, 1H), 5,99 (s a, 1H), 7,46 (s, 1H), 7,49 (d, 1H),7,55 (d, 1H), 7,88 (s, 3H).

Ejemplo 496

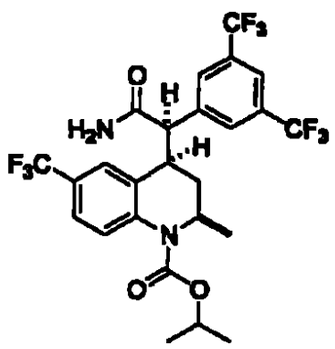


Éster isopropílico del ácido (*S, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 571 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,87 (m, 1H), 1,08 (d, 3H), 1,26 (d, 3H), 1,32 (d, 3H), 1,68 (m, 1H), 3,44 (t, 1H), 3,84 (d, 1H), 4,26 (m, 1H), 5,02 (m, 1H), 5,69 (s a, 1H), 6,01 (s a, 1H), 7,47 (s, 1H), 7,49 (d, 1H), 7,54 (d, 1H), 7,87 (s, 3H).

Ejemplo 497

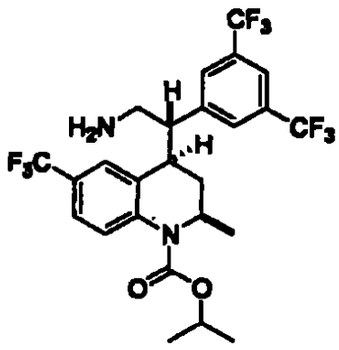


Éster isopropílico del ácido (*RS, RS, RS*) 4-[(3,5-bis-trifluorometil-fenil)-carbamoil-metil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 571 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,87 (m, 1H), 1,18 (d, 3H), 1,24 (d, 3H), 1,28 (d, 3H), 2,54 (m, 1H), 3,37 (t, 1H), 4,00 (d, 1H), 4,48 (m, 1H), 5,04 (m, 1H), 6,02 (s a, 1H), 6,33 (s a, 1H), 7,00 (s, 1H), 7,36 (d, 1H), 7,55 (d, 1H), 7,81 (s, 1H), 7,98 (s, 2H).

Ejemplo 498

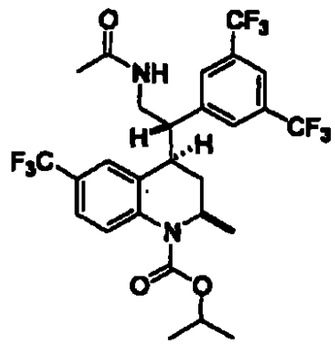


Éster isopropílico del ácido (*RS, RS, SR*) 4-[2-amino-1-(3,5-bis-trifluorometil-fenil)-etil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

LCMS (ESI+): 557 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,80 (m, 1H), 1,04 (d, 3H), 1,28 (d, 3H), 1,34 (d, 3H), 1,76 (m, 1H), 2,75(t, 1H), 3,11 (m, 1H), 3,35 (m, 1H), 3,46 (m, 1H), 4,26 (m, 1H), 5,06 (m, 1H), 7,54 (m, 3H), 7,7 (s, 2H), 7,84 (s, 1H).

Ejemplo 499

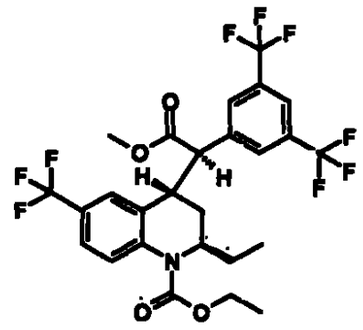


Éster isopropílico del ácido (*RS, RS, SR*) 4-[2-acetilamino-1-(3,5-bis-trifluorometil-fenil)-etil]-2-metil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

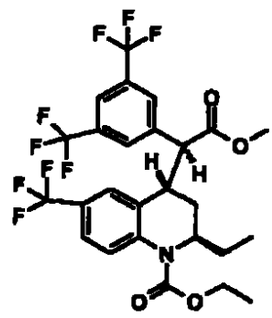
LCMS (ESI+): 599 (MH+)

^{1}H RMN ($CDCl_3$): □ 0,78 (m, 1H), 1,04 (d, 3H), 1,28 (d, 3H), 1,34 (d, 3H), 1,76 (m, 1H), 1,93 (s, 3H), 2,68 (s, 1H), 3,01 (m, 1H), 3,72 (m, 1H), 3,72 (m, 1H), 4,26 (m, 1H), 4,37 (m, 1H), 5,06 (m, 1H), 5,40 (m, 1H), 7,53 (s, 2H), 7,70 (s, 2H), 7,85 (s, 1H), 8,41 (s, 1H).

Ejemplos 500 y 501



Éster etílico del ácido (*R, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, S, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido 3,5-bis(trifluorometilfenil)acético (1,41 g, 4,93 mmol) en N,N-dimetilformamida anhidro (3 ml) se le añadió hidruro sódico (dispersión al 60% en aceite mineral, 6,55 mmol, 262 mg) y la mezcla se agitó a temperatura ambiente durante 60 minutos. Se añadió una solución de éster etílico de ácido (*R*) 4-cloro-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (1,10 g, 3,28 mmol, mezcla de isómeros, Preparación 14) en N,N-dimetilformamida anhidro (1,5 ml) y la mezcla se agitó a temperatura ambiente durante 72 horas. Se añadió agua (20 ml) y la mezcla se extrajo con éter dietílico (3 x 50 ml) y el extracto orgánico se secó sobre sulfato sódico anhidro y el disolvente se retiró al vacío para dar el producto en bruto en forma de un aceite amarillo (~2g). La purificación se realizó usando cromatografía radial (Chromatron modelo 7924T, Harrison Research, Palo Alto, CA) con un rotor de gel de sílice de 4 mm eluyendo con hexanos/acetato de etilo 9:1 para dar los compuestos del título:

Éster etílico del ácido (*R, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (diastereoisómero que eluye en primer lugar)

MS: 586,0 $[M+H]^+$ encontrado

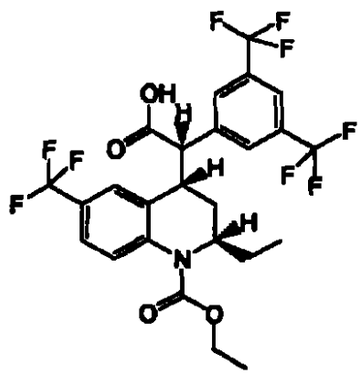
^{1}H RMN ($CDCl_3$) □ 7,90 (s, 2H), 7,87 (s, 1H), 7,59 (d, J = 8,30 Hz, 1H), 7.62 (d, J = 8,30 Hz, 1H), 7,61 (s, 1H), 4,39 - 4,27 (m, 2H9, 4,27-4,18 (m, 1H), 3,78 (d, J = 11,61 Hz, 1H), 3,59 (m, 1H), 3,48 (s, 3H), 1,76 (ddd, J = 14,10, 8,30, 3,30 Hz, 1H), 1,61-1,55 (m, 1H), 1,57-1,50 (m, 1H), 1,48-1,40 (m, 1H), 1,35 (t, J = 7,47 Hz, 3H), 0,73 (t, J = 7,47 Hz, 3H).

Éster etílico del ácido (*R, S, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (diastereoisómero que eluye en segundo lugar)

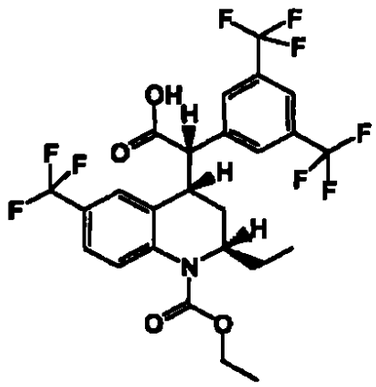
MS: 586,0 $[M+H]^+$ encontrado

^{1}H RMN ($CDCl_3$) □ 7,66 (s, 1H), 7,42 (d, J = 8,30 Hz, 1H), 7,40 (s, 2H), 7,3 (dd, J = 8,30, 1,66 Hz, 1H), 6,47 (d, J = 1,66 Hz, 1H), 4,55-4,47 (m, 1H), 4,34 (m, 1H), 4,32 (m, 1H), 3,83 (d, J = 11,61 Hz, 1H), 3,80 (s, 3H), 3,43 (ddd, J = 11,61, 4,98, 2,49 Hz, 1H), 2,44 (ddd, J = 14,11, 8,30, 2,49 Hz, 1H), 1,81 (ddd, J = 14,10, 8,30, 4,98 Hz, 1H), 1,67 (m, 1H), 1,51 (m, 1H), 1,33 (t, J = 7,47 Hz, 3H), 0,85 (t, J = 7,47 Hz, 3H).

Ejemplos 502 y 503



Éster etílico del ácido (*R, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, S, S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Una mezcla de éster etílico del ácido (*R, S, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplo 501, 100 mg, 0,171 mmol), hidróxido sódico acuoso (2N, 0,512 ml, 1,024 mmol) y tetrahidrofurano anhidro (2 ml) se agitó a temperatura ambiente durante 2 días antes de añadir ácido clorhídrico 2N (1,5 ml). La mezcla se diluyó con acetonitrilo y se evaporó a sequedad al vacío para dar el producto bruto en forma de un aceite (128 mg). La purificación se realizó usando cromatografía radial (Chromatron modelo 7924T, Harrison Research, Palo Alto, CA) con un rotor de gel de sílice de 4 mm eluyendo con hexanos/acetato de etilo 55:45 para dar los compuestos del título:

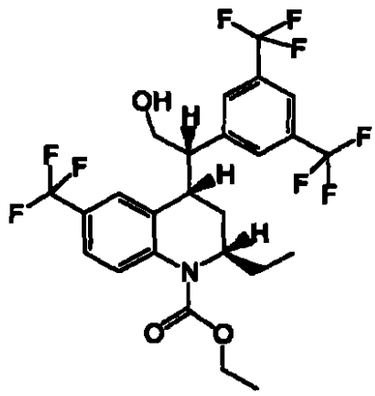
Compuesto que eluye en primer lugar: éster etílico del ácido (*R, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (14 mg);

^{1}H RMN ($CDCl_3$) □ 7,88 (s, 1H), 7,88 (s, 2H), 7,55 (m, 1H), 7,51 (m, 1h), 7,49 (m,1 H), 4,32 (m, 1h), 4,27 (m, 1H), 4,21 (m, 1H), 3,80 (d, J = 10,79 Hz, 1H), 3,57 (m, 1H, 1,78 (m, 1H), 1,55 (m, 2H), 1,43 (m, 1H), 1,32 (t, J = 7,47 Hz, 3H), 0,71 (t, J = 7,47 Hz, 3H).

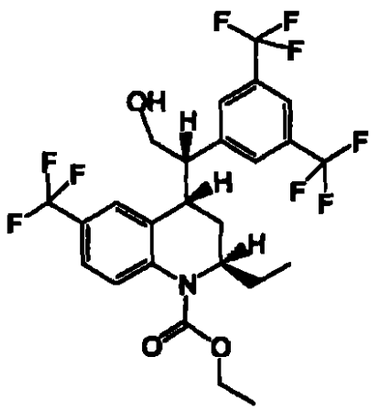
Compuesto que eluye en segundo lugar: éster etílico del ácido (*R, S, S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (32 mg)

^{1}H RMN ($CDCl_3$) □ 7,67 (s, 1H), 7,45 (s, 2H), 7,41 (m, 1H), 7,34 (m, 1H), 6,51 (s a, 1H), 4,55 (m, 1H), 4,32 (m, 2H), 3,85 (d, J = 10,79 Hz, 1H), 3,43 (m, 1H), 2,55 (m, 1H), 1,81 (m, 1H), 1,63 (m, 1H), 1,60 (m, 1H), 1,31 (t, J = 7,47 Hz, 3H), 0,84 (t, J = 7,47 Hz, 3H).

Ejemplos 504 y 505



Éster etílico del ácido (*R, S, R*) 4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico



Éster etílico del ácido (*R, S, S*) 4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

A una solución de éster etílico del ácido (*R, S, R*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico y éster etílico del ácido (*R, S, S*) 4-[(3,5-bis-trifluorometil-fenil)-carboxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (Ejemplos 502 y 503 como se han preparado anteriormente pero sin separar los isómeros, 143 mg, 0,25 mmol) en tetrahidrofurano (3 ml) en una atmósfera de nitrógeno se le añadió un complejo de borano-dimetilsulfuro (2M en tetrahidrofurano, 0,25 ml, 0,5 mmol). Después de 24 horas la mezcla se diluyó con metanol (1 ml) y se evaporó a sequedad al vacío. Al residuo se le añadió ácido clorhídrico 2N (3ml). La mezcla se agitó durante 10 minutos y después se extrajo con éter dietílico (3 x 15 ml). La capa orgánica se secó sobre sulfato sódico anhidro y el disolvente se evaporó al vacío para dar el producto en bruto en forma de un aceite (175mg). La purificación se realizó usando cromatografía radial (Chromatron modelo 7924T, Harrison Research, Palo Alto, CA) con un rotor de gel de sílice de 1 mm eluyendo con un gradiente de hexanos/acetato de etilo de 4:1 a7:3 para dar los compuestos del título:

Compuesto que eluye en primer lugar: Éster etílico del ácido (*R, S, R*) 4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (9 mg)

MS: 558,3 $[M+H]^+$ encontrado.

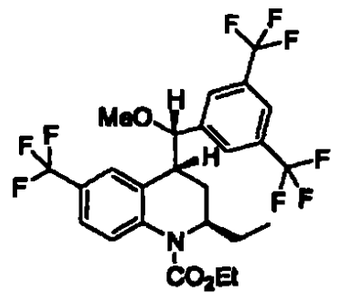
^{1}H RMN ($CDCl_3$): □ 7,83 (s, 1h), 7,79 (s, 2H), 7,60 (m, 1H), 7,53 (s a, 1H), 7,52 (m, 1H), 4,35 (m, 1H), 4,24 (m, 1H), 4,16 (m, 1H), 3,71, (m, 2H), 3,34 (m, 1H), 2,99 (m, 1H), 1,78 (m, 1H), 1,57 (m, 2H), 1,57 (m, 1H), 1,45 (m, 1H), 1,33 (t, J = 7,47 Hz, 3H), 0,71 (t, J = 7,47 Hz, 3H).

Compuesto que eluye en segundo lugar: Éster etílico del ácido (*R, S, S*) 4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

MS: 558,5 $[M+H]^+$ encontrado.

^1H RMN ($CDCl_3$): □ 7,63 (s, 1H), 7,40 (m, 1H), 7,39 (s, 2H), 7,32 (m, 1H), 6,62 (s a, 1H), 4,48 (m, 1H), 4,25 (m, 2H), 4,15 (m, 2H), 3,13 (m, 2H), 2,60 (m, 1H), 1,69 (m, 3H), 1,50 (m, 1H), 1,29 (t, J = 7,47Hz, 3H), 0,86 (t, J = 7,47 Hz, 3H).

Ejemplo 506



Éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-metoxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico

Se introdujo éster etílico del ácido (*R, R, S*) 4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico (0,030 g, 0,055 mmol, 1 eq) en un matraz de fondo redondo equipado con una barra de agitación magnética. Se añadió DMSO (1,0 ml) seguido de la adición de (0,012 g, 0,221 mmol, 4 eq) de hidróxido de potasio y (0,016 g, 0,110 mmol, 2 eq) de yoduro de metilo a temperatura ambiente. Después de 1,5 horas, la mezcla de reacción se inactivó con HCl 1N, se extrajo tres veces con acetato de etilo y se secó sobre sulfato sódico anhidro. El material en bruto se purificó por cromatografía en gel de sílice para proporcionar el compuesto del título. LCMS (ESI+): 551 (MH+).

^{1}H RMN ($CDCl_3$): □ 0,95 (t, 3H), 1,31 (t, 3H), 1,41 (m, 1H), 1,60 (m, 1H), 2,6 (m, 1H), 2,90 (m, 1H), 3,20 (s, 3H), 4,33 (m, 2H), 4,45 (m, 1H), 6,60 (s, 1H), 7,2 (s, 2H), 7,30 (d, 1H), 7,5 (d, 1H), 7,70 (s, 1H).

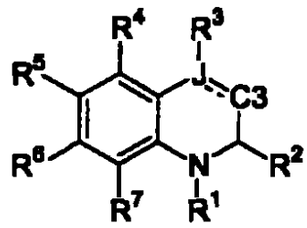
A lo largo de esta solicitud se hace referencia a diversas publicaciones. Las descripciones de estas publicaciones se incorporan en su totalidad en esta solicitud en todos los sentidos.

Será evidente para los especialistas en la técnica que se pueden realizar diversas modificaciones y variaciones en la presente invención sin desviarse del alcance o espíritu de la invención. Otras realizaciones de la invención serán evidentes para los especialistas en la técnica a partir de la consideración y la práctica de la invención descrita en este documento. Se pretende que la memoria descriptiva y los ejemplos se consideren exclusivamente como ejemplos, indicándose el verdadero alcance y espíritu de la invención por medio de las siguientes reivindicaciones.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1.- Un compuesto de acuerdo con la Fórmula I



Fórmula I

en la que

C3 es carbono;

J es nitrógeno o carbono, donde si J es carbono, entonces el enlace entre C3 y J es un enlace sencillo o doble y si J es nitrógeno, entonces el enlace entre C3 y J es un enlace sencillo;

R^1 es Y, W-X o W-Y^1; donde W es un carbonilo, tiocarbonilo, sulfinilo o sulfonilo; X es -O-Y, -S-Y, -N(H)-Y o -N-$(Y)_2$; Y para cada caso es independientemente Z o una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a diez miembros, lineal o ramificada, donde cada carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con uno o dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente sustituido con oxo, estando dicho azufre opcionalmente mono- o di-

sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con oxo y estando dicha cadena carbonada opcionalmente mono-sustituida con Z; e Y^1 para cada caso es independientemente Z o una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a diez miembros, lineal o ramificada, donde cada carbono distinto del carbono de unión, puede reemplazarse opcionalmente con uno o dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente sustituido con oxo, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con oxo y estando dicha cadena carbonada opcionalmente mono-sustituida con Z; donde Z es un anillo de tres a ocho miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente Z está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquenilo (C_2-C_6), alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) estando dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6)

opcionalmente sustituido con uno a nueve átomos de flúor;

R^2 es una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, donde cada carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con uno o dos heteroátomos seleccionados independientemente entre oxígeno y azufre y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicha cadena carbonada opcionalmente mono-sustituida con oxo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho azufre opcionalmente mono- o di-sustituido con oxo; o dicho R^2 es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a siete miembros que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno y azufre, donde dicho anillo R^2 está opcionalmente unido mediante un alquilo (C_1-C_4); donde dicho anillo R^2 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquenilo (C_2-C_6), alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), oxo o alquiloxicarbonilo (C_1-C_6);

R^3 es una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, que contiene C4a, donde C4a es un átomo de carbono que conecta con J, donde cada carbono de la cadena carbonada puede reemplazarse opcionalmente con un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno donde dicho carbono está opcionalmente mono-, di- o tri-sustituido con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con oxo o nitrógeno, estando dicho

azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo y estando dicha cadena carbonada mono, di- o tri-sustituida con V en C4a en el carbono R^3 adyacente a C4a; siempre que en R^3, cuando J es carbono, sea distinto de C4a que está opcionalmente reemplazado con un heteroátomo; y siempre que en R^3, cuando J es nitrógeno, sea distinto de C4a que está opcionalmente reemplazado con un heteroátomo y sea distinto de C4a que está opcionalmente mono-sustituido con hidroxi o nitrógeno; donde V es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a ocho miembros que tiene opcionalmente de uno o cuatro heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno tal que V no es imidazolilo o un anillo heterocíclico totalmente saturado que contiene nitrógeno donde el nitrógeno del anillo está unido al grupo R^3; un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; o un anillo tricíclico que consiste en tres anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente V está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con V^1, alquil (C_1-C_6)-V^1, C(O)-V^1, O-alquil (C_0-C_6)-V^1, alquil (C_1-C_6)-O-V^1, C(O)-mono-N- o di-N,N-alquil (C_1-C_6)-V^1, halo, alquilo (C_1-C_6), alquenilo (C_2-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), alquilsulfinilo (C_1-C_4), alquilsulfonilo (C_1-C_4), mono-N- o di-N,N-alquilsulfonilo (C_1-C_6), amino, nitro, ciano, oxo, carboxamoílo, mono-N- o di-N,N-alquilcarboxamoílo (C_1-C_6), carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-

alquilamino (C_1-C_6), donde dicho sustituyente alquilo (C_1-C_6) o alquenilo (C_2-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6), donde cada uno de los sustituyentes alquilo (C_1-C_6), alcoxi (C_1-C_6), alquiltio (C_1-C_4), alquilsulfonilo (C_1-C_4) o alquenilo (C_2-C_6) también están opcionalmente sustituidos con uno a nueve átomos de flúor; donde V^1 es un anillo de tres a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente V^1 está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con halo, alquilo (C_1-C_6), alcoxi (C_1-C_6), hidroxi, oxo, amino, nitro, ciano, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-sustituido con oxo, dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) también está opcionalmente sustituido con uno a nueve átomos de flúor; y

cada uno de R^4, R^5, R^6 y R^7 es independientemente hidrógeno, un enlace, nitro o halo donde dicho enlace está sustituido con T o una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada (C_1-C_{12}), lineal o ramificada, donde cada carbono puede reemplazarse opcionalmente con uno o dos heteroátomos por cadena carbonada donde los heteroátomos se seleccionan independientemente entre oxígeno, azufre y nitrógeno, donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con

hidroxi, estando dicho carbono opcionalmente mono-sustituido con oxo o nitrógeno, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo y estando dicha cadena carbonada opcionalmente mono-sustituida con T; donde T es un anillo de tres a doce miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno o un anillo bicíclico que consta de dos anillos condensados de tres a seis miembros condensados parcialmente saturados, totalmente saturados o totalmente insaturados, tomados independientemente, que tienen opcionalmente de uno a cuatro heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; y dicho sustituyente T está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), alquenilo (C_2-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) teniendo dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) opcionalmente de uno a nueve átomos de flúor;

R^4 y R^5, R^5 y R^6, y/o R^6 y R^7 opcionalmente se pueden tomar conjuntamente y formar al menos un anillo que es un anillo parcialmente saturado o totalmente insaturado de cuatro a ocho miembros que tiene opcionalmente de uno a tres heteroátomos seleccionados independientemente entre nitrógeno, azufre y oxígeno; donde cada uno de los anillo formados por R^4 y R^5 o R^5 y R^6, y/o R^6 y R^7 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), alquilsulfonilo (C_1-C_4), alquenilo (C_2-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi,

alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) está opcionalmente mono-, di- o tri-sustituido independientemente con hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, nitro, ciano, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) teniendo dicho sustituyente alquilo (C_1-C_6) opcionalmente de uno a nueve átomos de flúor;

o una sal o profármaco farmacéuticamente aceptable del mismo;

con las siguientes condiciones:

a) cuando hay un sencillo doble entre C3 y J y R^3 es una cadena carbonada totalmente saturada de uno a seis miembros lineal o ramificada sustituida en C4a con V entonces R^1 es distinto de C(O)-alquilo (C_1-C_4) opcionalmente mono-, di- o tri-sustituido con halo y R^1 es distinto de un anillo C(O)-monociclicaromático; o

b) cuando hay un enlace sencillo entre C3 y J, y R^3 es -C(O)-O-V, y R^2 es fenilo entonces R^1 es distinto de alquilo (C_1-C_4); y

c) cuando hay un enlace doble entre C3 y J, y R^2 es metilo entonces R^3 es distinto de $-CH_2$-O-V, $-CH_2$-V o $-CH_2-CH_2$-V.

2.- Un compuesto de la reivindicación 1 donde

J es carbono;

R^1 es W-X;

W es carbonilo;

X es -O-Y;

Y para cada caso es independientemente alquilo (C_1-C_6), teniendo opcionalmente dicho alquilo (C_1-C_6) de uno a nueve átomos de flúor o estando dicho alquilo (C_1-C_6) opcionalmente mono-sustituido con Z;

donde Z es un anillo parcialmente saturado, totalmente saturado o totalmente

insaturado de tres a seis miembros que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente Z está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), alquiltio (C_1-C_4), nitro, ciano, oxo o alquiloxicarbonilo (C_1-C_4), estando dicho alquilo (C_1-C_4) o alcoxi (C_1-C_4) opcionalmente sustituido con uno a nueve átomos de flúor;

R^2 es beta y es una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada (C_1-C_4), lineal o ramificada, donde un carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con oxígeno o azufre y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicha cadena carbonada opcionalmente mono-sustituida con oxo o hidroxi, estando dicho azufre opcionalmente mono- o di-sustituido con oxo; o dicho R^2 es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a cinco miembros que tiene opcionalmente un heteroátomo seleccionado independientemente entre oxígeno y azufre,

donde dicho anillo R^2 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), amino, nitro, alquiloxicarbonilo (C_1-C_4) o carboxi;

donde R^3 es una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, donde cada carbono, distinto de C4a puede reemplazarse opcionalmente con un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno, y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con ciano, estando dicho carbono opcionalmente mono-sustituido con oxo o nitrógeno, estando dicho

azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo y estando dicha cadena carbonada opcionalmente mono, di- o tri-sustituida con V en C4a en el carbono R^3 adyacente a C4a; V es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres, cuatro, cinco o seis miembros que tiene opcionalmente de uno o tres heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno tal que V no es imidazolilo o un anillo heterocíclico totalmente saturado que contiene nitrógeno donde el nitrógeno del anillo está unido al grupo R^3;

donde dicho anillo V está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxicarbonilo (C_1-C_6), nitro, ciano u oxo, donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

R^4 es hidrógeno;

Cada uno de R^5 y R^6 son independientemente hidrógeno, halo, T, alcoxi (C_1-C_6) o alquilo (C_1-C_6), teniendo dicho sustituyente alcoxi (C_1-C_6) o alquilo (C_1-C_6) opcionalmente de uno a nueve átomos de flúor o estando dicho alcoxi (C_1-C_6) o alquilo (C_1-C_6) opcionalmente mono-sustituido con T;

donde T es un anillo de cinco a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente T está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor; y

R^7 es hidrógeno;

o una sal farmacéuticamente aceptable del mismo.

3.- Un compuesto de la reivindicación 2 donde

Y es metilo, etilo, 1-propilo, 2-propilo o terc-butilo;

R^2 es metilo, etilo, 2-propilo, ciclopropilo o ciclobutilo;

R^3 es -C(O)-V, -C(OC)(C(O)OCH_3)(V), -CH(F)(V), -CF_2(V), -CH(OCH_3)(V), -CH(C(O)OCH_3)(V), -CH(CN)(V), -CH(OH)(V), -CH_2(V), -CH(NH_2)(V), -CH(NH(CH_3)(V), -CH(C(O)NH_2)(V), -CH(CH_2OH)(V), -CH(CH_2OCH_3)V, -CH($CH_2OC(O)CH_3$)V, -CH(CH_2FV), o -CH(CH_2 NH_2)V; y

V es fenilo opcionalmente mono-, di- o tri-sustituido independientemente con halo, nitro o alquilo (C_1-C_2) donde dicho sustituyente alquilo (C_1-C_2) tiene opcionalmente de uno a cinco átomos de flúor;

Cada uno de R^5 y R^6 son independientemente hidrógeno, metilo, metoxi o cloro; teniendo dicho metoxi opcionalmente de uno a tres átomos de flúor, teniendo dicho metilo opcionalmente de uno a tres átomos de flúor;

o una sal farmacéuticamente aceptable del mismo.

4.- Un compuesto de la reivindicación 3 donde

Y es etilo;

R^2 es etilo o metilo;

R^3 es (3,5-bis-(trifluorometil)-fenil)-hidroxi-metoxicarbonil-metilo; (3,5-bis-trifluorometil-fenil)-metoxicarbonil-metilo; (3,5-bis-trifluorometil-fenil)-ciano-metilo, 3,5-bis-trifluorometil-benzoílo; (3,5-bis-trifluometil-fenil)-hidroxi-metilo; (3,5-bis-trifluorometil-fenil)-fluoro-metilo; (3,5-bis-trifluorometil-fenil)-difluoro-metilo; (3,5-bis-

(trifluorometil)-bencilo); (3,5-bis-trifluorometil-fenilcarbamoil)-metilo; amino-(3,5-bis-(trifluorometil)-fenil)-metilo; (3,5-bis-(trifluorometil)-fenil)-metilamina-metilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-amino-etilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-fluoro-etilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-metoxi-etilo; 1-(3,5-bis-(trifluorometil)-fenil)-2-hidroxi-etilo; o 2-acetoxi-1-(3,5-bis-(trifluorometil)-fenil)-etilo;

R^5 es metoxi o trifluorometilo; y

R^6 es hidrógeno o metoxi;

o una sal farmacéuticamente aceptable del mismo.

5.- Un compuesto de la reivindicación 1 donde

J es nitrógeno;

el enlace entre C3 y J es un enlace sencillo;

R^1 es W-X;

W es carbonilo;

X es -O-Y;

Y para cada caso es independientemente alquilo (C_1-C_6), teniendo opcionalmente dicho alquilo(C_1-C_6) de uno a nueve átomos de flúor o estando dicho alquilo (C_1-C_6) opcionalmente mono-sustituido con Z;

donde Z es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a seis miembros que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente Z está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), alquiltio (C_1-C_4), nitro, ciano, oxo o alquiloxicarbonilo (C_1-C_4), estando dicho alquilo (C_1-C_4) o alcoxi (C_1-C_4) opcionalmente sustituido con uno a nueve átomos de flúor;

R^2 es una cadena carbonada parcialmente saturada, totalmente saturada o totalmente insaturada (C_1-C_4), lineal o ramificada, donde un carbono, distinto del carbono de unión, puede reemplazarse opcionalmente con oxígeno o azufre y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicha cadena carbonada opcionalmente mono-sustituida con oxo, estando dicho carbono opcionalmente mono-sustituido con hidroxi, estando dicho azufre opcionalmente mono- o di-sustituido con oxo; o dicho R^2 es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de tres a cinco miembros que tiene opcionalmente un heteroátomo seleccionado independientemente entre oxígeno y azufre; donde dicho anillo R^2 está opcionalmente mono-, di- o tri-sustituido independientemente con halo, hidroxi, alcoxi (C_1-C_6), amino, nitro, alquiloxicarbonilo (C_1-C_4) o carboxi;

R^3 es una cadena carbonada totalmente saturada, parcialmente insaturada o totalmente insaturada de uno a seis miembros, lineal o ramificada, donde cada carbono, distinto de C4a o del carbono R^3 adyacente a C4a, puede reemplazarse opcionalmente con un heteroátomo seleccionado entre oxígeno, azufre y nitrógeno, y donde dicho carbono está opcionalmente mono-, di- o tri-sustituido independientemente con halo, estando dicho carbono, distinto de C4a, opcionalmente mono-sustituido con hidroxi, estando dicho carbono opcionalmente mono-sustituido con ciano, estando dicho carbono opcionalmente mono-sustituido con oxo o nitrógeno, estando dicho azufre opcionalmente mono- o di-sustituido con oxo, estando dicho nitrógeno opcionalmente mono- o di-sustituido con hidrógeno u oxo y estando dicha cadena carbonada opcionalmente mono, di- o tri-sustituida con V en C4a en el carbono R^3 adyacente a C4a;

V es un anillo parcialmente saturado, totalmente saturado o totalmente insaturado de cinco o seis miembros que tiene opcionalmente de uno a tres heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno tal que V no es

imidazolilo o un anillo heterocíclico totalmente saturado que contiene nitrógeno donde el nitrógeno del anillo está unido al grupo R^3; donde dicho anillo V está opcionalmente mono-, di-, tri-, tetra- o penta-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alcoxicarbonilo (C_1-C_6), nitro, ciano u oxo, donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

R^4 es hidrógeno;

Cada uno de R^5 y R^6 son independientemente hidrógeno, halo, T, alcoxi (C_1-C_6) o alquilo (C_1-C_6), teniendo opcionalmente dicho sustituyente alcoxi (C_1-C_6) o alquilo (C_1-C_6) de uno a nueve átomos de flúor o estando dicho alcoxi (C_1-C_6) o alquilo (C_1-C_6) opcionalmente mono-sustituido con T;

donde T es un anillo de cinco a seis miembros parcialmente saturado, totalmente saturado o totalmente insaturado que tiene opcionalmente de uno a dos heteroátomos seleccionados independientemente entre oxígeno, azufre y nitrógeno;

donde dicho sustituyente T está opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), alquiltio (C_1-C_4), amino, oxo, carboxi, alquiloxicarbonilo (C_1-C_6), mono-N- o di-N,N-alquilamino (C_1-C_6) donde dicho sustituyente alquilo (C_1-C_6) o alcoxi (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

R^7 es hidrógeno;

o una sal farmacéutica mente aceptable del mismo.

6.- Un compuesto de la reivindicación 5 donde

Y es alquilo (C_1-C_4), donde dicho sustituyente alquilo (C_1-C_4) tiene opcionalmente de uno a nueve átomos de flúor;

R^2 es alquilo (C_1-C_4), ciclopropilo o ciclobutilo;

R^3 es -C(O)-V, -CH(C(O)O(alquil (C_1-C_3))(V) o -CH(CN)(V);

V es fenilo opcionalmente mono-, di- o tri-sustituido independientemente con halo, alquilo (C_1-C_6), hidroxi, alcoxi (C_1-C_6), nitro, ciano u oxo donde dicho sustituyente alquilo (C_1-C_6) tiene opcionalmente de uno a nueve átomos de flúor;

Cada uno de R^5 y R^6 son independientemente hidrógeno, alcoxi (C_1-C_3) o alquilo (C_1-C_6), teniendo opcionalmente dicho sustituyente alcoxi (C_1-C_3) de uno a nueve átomos de flúor, teniendo dicho sustituyente alquilo (C_1-C_6) opcionalmente de uno a siete átomos de flúor;

o una sal farmacéuticamente aceptable del mismo.

7.- Un compuesto de la reivindicación 6 donde

Y es metilo, etilo, 1-propilo, 2-propilo o terc-butilo;

R^2 es metilo, etilo, 2-propilo, ciclopropilo o ciclobutilo;

R^3 es 3,5-bis-trifluorometil-benzoílo, (3,5-bis-trifluorometil-fenil)-ciano-metilo o (3,5-bis-trifluorometil-fenil)-metoxicarbonil-metilo;

R^5 es metilo o trifluorometilo;

R^6 es hidrógeno o metilo.

8.- Un compuesto de acuerdo con la reivindicación 1, seleccionado entre el grupo compuesto por:

Éster etílico del ácido (*R, R, S*)-4-[Amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[Amino-(3,5-bis-trifluorometil-fenil)-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-(3,5-bis-trifluorometil-bencil)-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metilaminometil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metilaminometil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-

metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolina-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxil-metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-hidroxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[2-Acetoxi-1-(3,5-bis-trifluorometil-fenil)-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[2-Acetoxi-1-(3,5-bis-trifluorometil-fenil)-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-metoxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-metoxi-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-fluoro-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-fluoro-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-amino-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[1-(3,5-bis-trifluorometil-fenil)-2-amino-etil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6-trifluorometil-2H-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-(3,5-bis-trifluorometil-benzoil)-6,7-dimetoxi-2-

metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-(3,5-bis-trifluorometil-benzoil)-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-fluoro-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*)-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*)-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *R*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-6,7-dimetoxi-2-metil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*, *S*, *S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, S, R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R, R, S*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico; y

Éster etílico del ácido (*R, R, R*)-4-[(3,5-bis-trifluorometil-fenil)-hidroxi-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinolin-1-carboxílico;

Éster etílico del ácido (*R*)-4-(3,5-bis-trifluorometil-benzoil)-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-ciano-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster metílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster metílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster isopropílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster isopropílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6,7-dimetil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

Éster etílico del ácido (*R, R*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-

metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico; y

Éster etílico del ácido (*R, S*)-4-[(3,5-bis-trifluorometil-fenil)-metoxicarbonil-metil]-2-etil-6-trifluorometil-3,4-dihidro-2*H*-quinoxalin-1-carboxílico;

o una sal o profármaco farmacéuticamente aceptable de los mismos.

9.- Un procedimiento para tratar aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio en un mamífero administrando a un mamífero en necesidad de tal tratamiento una cantidad para tratar aterosclerosis, enfermedad de la arteria coronaria, enfermedad cardíaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar o infarto de miocardio de un compuesto de cualquiera de las reivindicaciones 1 a 8, un profármaco del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco.

10.- Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1 a 8, un profármaco del mismo o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco y un vehículo, diluyente o excipiente farmacéuticamente aceptable.

11.- Una combinación farmacéutica que comprende: una cantidad terapéuticamente eficaz de una composición que comprende

un primer compuesto, siendo dicho primer compuesto un compuesto de

cualquiera de las reivindicaciones 1 a 8, un profármaco del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco;

un segundo compuesto, siendo dicho segundo compuesto un inhibidor de la HMG CoA reductasa, un inhibidor de la secreción de MTP/Apo B, un modulador de PPAR, un inhibidor de la recaptación de ácidos biliares, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, niacina de liberación lenta, una combinación de niacina y lovastatina, una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT o un secuestrador de los ácidos biliares; y

un vehículo, diluyente o excipiente farmacéutico.

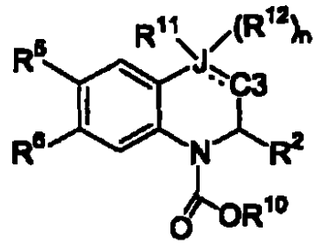
12.- Una combinación farmacéutica como se indica en la reivindicación 11 en la que el segundo compuesto es un inhibidor de la HMG-CoA reductasa o un modulador de PPAR.

13.- Una combinación farmacéutica como se indica en la reivindicación 12 en la que el segundo compuesto es lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, rosuvastatina o pitavastatina.

14.- Un kit para conseguir un efecto terapéutico en un mamífero que comprende, envasados conjuntamente con un primer agente terapéutico que comprende una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las reivindicaciones 1 a 8, un profármaco del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco y un vehículo farmacéuticamente aceptable, un segundo agente terapéutico que comprende una cantidad terapéuticamente

eficaz de un inhibidor de la HMG CoA reductasa, un modulador de PPAR, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, niacina de liberación lenta, una combinación de niacina y lovastatina, una resina de intercambio iónico, un antioxidante, un inhibidor de la ACAT o un secuestrador de los ácidos biliares y un vehículo farmacéuticamente aceptable e instrucciones para la administración de dicho primer y segundo agente para conseguir el efecto terapéutico.

15.- Un compuesto de Fórmula III



Fórmula III

en la que

C3 es carbono;

J es carbono, donde el enlace entre C3 y J es un enlace sencillo o doble;

n es cero si el enlace entre C3 y J es un enlace doble o uno si el enlace entre C3 y J es un enlace sencillo;

R^2 es alquilo (C_1-C_4), ciclopropilo o ciclobutilo;

R^5 es CF_3;

R^6 es hidrógeno;

R^{10} es una cadena carbonads totalmente saturada (C_1-C_4) lineal o ramificada;

R^{11} es halo, hidroxi, -C(O)(O alquilo (C_1-C_4)), -C(O)C(O)(O alquilo (C_1-C_4)), –

C(O)NH(O alquilo (C_1-C_4)) o -C(O)N((alquilo (C_1-C_4))(O alquilo (C_1-C_4));

R^{12} es hidrógeno o halo, donde R^{11} no es halo cuando R^{12} es halo;

o R^{11} y R^{12} se toman conjuntamente para formar oxo o N_2;

o una sal o profármaco farmacéuticamente aceptable del mismo.

RESUMEN

Compuestos de quinolina y quinoxalina, composiciones farmacéuticas que contienen tales compuestos y el uso de tales compuestos para aumentar ciertos niveles de lípidos en el plasma, incluyendo la lipoproteína de alta densidad del colesterol y para reducir otros niveles de lípidos en plasma, tales como colesterol LDL y triglicéridos, y por consiguiente, para tratar enfermedades que se ven afectadas por los niveles bajos de colesterol HDL y/o niveles altos de colesterol-LDL y triglicéridos, tales como aterosclerosis y enfermedades cardiovasculares en ciertos mamíferos, incluyendo seres humanos.

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TRATAD DE COOPERACIÓN DE PATENTES
PCT
NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL
(PCT Regla 71.1)
De: AUTORIDAD DE REVISION PRELIMINAR INTERNACIONAL

Para:
LUMB, J. Trevor
PFIZER INC
c/o Jackie Lawrence
Eastern Point Road,
Mailstop 8260-1615
Groton, Connecticut 06340
Estados Unidos de América

Sello de recibido de fecha 18 de febrero de 2005 Pfizer Inc.

Fecha de expedición: 15.02.2005
Referencia del expediente del solicitante o mandatario: PC25623A
Solicitud Internacional No.: PCT/IB2004/000836
Fecha de presentación internacional: 15.03.2004
Fecha de prioridad: 28.03.2003
Solicitante: PFIZER PRODUCTS INC. ET. AL..

1. Se notifica al solicitante que la Administración Encargada del Examen Preliminar Internacional ha emitido el informe de examen preliminar internacional para la solicitud internacional y se lo transmite adjunto, acompañado, si procede, de sus anexos.

2. Se transmite una copia del presente informe y, si procede, de sus anexos, a la Oficina Internacional para comunicación a todas las Oficinas elegidas.

3. Si alguna Oficina elegida lo exige, la Oficina Internacional realizará una traducción en inglés del informe (con exclusión de sus anexos) y la transmitirá a las Oficinas interesadas.

4. **RECORDATORIO**

   Para iniciar la fase nacional ante cada Oficina elegida, el solicitante debe cumplir ciertos actos (presentación de la traducción y pago de las tasas nacionales) en el plazo de 30 meses desde la fecha de prioridad (o más tarde por lo que respecta a ciertas oficinas) (Artículo 39.1) (véase también el recordatorio enviado por la Oficina Internacional en el formulario PCT/IB/301).

Cuando deba entregarse una traducción de la solicitud internacional o una oficina elegida, se incluirá la traducción de cualquier anexo de informe de Examen Preliminar Internacional. Corresponde al solicitante preparar la traducción en cuestión y entregarla directamente a cada Oficina elegida interesada

Para más amplios detalles en lo relativo a los plazos aplicables y las exigencias de las oficinas elegidas, véase el volumen II de la guía del solicitante PCT.

Se llama la atención del solicitante sobre el Artículo 33(5) que prevé que los criterios de novedad, actividad inventiva y de aplicación industrial definidos en el Artículo 33(2) a (4) sólo servirán a los efectos del examen preliminar internacional, y que "todo Estado contratante puede aplicar criterios adicionales o diferentes al objeto de decidir, en ese Estado, si la invención es patentable o no" (véase también el Artículo 27(5)). Tales criterios adicionales pueden afectar, por ejemplo, a las excepciones de patentabilidad, requisitos específicos relativos a la divulgación, la claridad de las reivindicaciones.

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea
D-80298 – Munich
Tel: +49-89 2399 - 0, Tx: 523656 epmu d
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Funcionario Autorizado: Ambroa, J.R.
Tel: + 49 89 2399-8012

TRATAD DE COOPERACIÓN DE PATENTES
PCT
INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperación en materia de Patentes)
(PCT Artículo 36 y Regla 70)

Referencia del expediente del solicitante o mandatario: PC25623A
Solicitud Internacional No.: PCT/IB2004/000836
Fecha de presentación internacional: 15.03.2004
Fecha de prioridad: 28.03.2003
Clasificación Internacional de Patentes (IPC) o la vez clasificación nacional e IPC: C07D215/14, C07D215/50, C07D215/12, C07D241/42, C07D401/04, C07D401/12, C07D409/12, C07D405/12, C07D413/12, C07D417/12, C07D403/06, C07D401/06, C07D413/06, C07D405/06, C07D417/06, C07D409/06, A61K31/47, A61K31/4709, A61K31/517, A61P9/10, A61P3/04, A61P3/10.
Solicitante: PFIZER PRODUCTS INC. et. al.

1. El presente informe preliminar internacional sobre patentabilidad, se establece por esta Administración encargada del examen preliminar internacional según el Artículo 35 y se transmite al solicitante conforme el Artículo 36.

2. Este INFORME consta de un total de 8 hojas, incluida la presente hoja de portada.

3. Este informe también contiene ANEXOS, que comprenden.
   a. ☐ (*remitido al solicitante y a la oficina internacional*) un total de _ hojas,
      descritas a continuación:
      ☐ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administración (véase la Regla 70.16 y la Instrucción Administrativa 607 del PCT).

      ☐ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, según se indica en el punto 4 del Reglamento I y en el Recuadro Suplementario.
   b. ☐ (remitido únicamente a la Oficina Internacional) un total de (indicar tipo y soporte(s) electrónico(s)) , que contienen una lista de secuencias y/o tabla(s) relativa(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo

a Listas de Secuencias (ver Instrucción Administrativa 802).

4. El presente informe contiene indicaciones relativas a los siguientes puntos:

☒	Recuadro I	Base de este informe
☐	Recuadro II	Prioridad
☒	Recuadro III	Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial
☒	Recuadro IV	Falta de unidad de Invención
☒	Recuadro V	Declaración motivada según el Artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones en apoyo de esta declaración
☐	Recuadro VI	Ciertos documentos citados
☐	Recuadro VII	Defectos en la Solicitud Internacional
☐	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de radicación de la demanda: 06.05.2004
Fecha de elaboración de este reporte: 15.02.2005

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea
D-80298 – Munich
Tel: +49-89 2399 - 0, Tx: 523656 epmu d
Fax: +49-89 2399 – 4465.

Funcionario Autorizado: Cortés, J.
Tel: + 49 89 2399-8206

Recuadro No. I Base de este informe

1. Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada a continuación.

☐ Este informe está basado en una traducción del idioma original al siguiente idioma____, que es el de una traducción proporcionada a los fines de:
- ☐ búsqueda internacional (según Reglas 12.3 y 23.1 (b))
- ☐ publicación de la solicitud internacional (según Regla 12.4)
- ☐ examen preliminar internacional (según Reglas 55.2 y/o 55.3)

2. Por lo que respecta a los **elementos** de la solicitud internacional, esta opinión se ha establecido sobre la base de (*las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe):*

Descripción, Páginas

1-310 tal como se presentaron inicialmente

Reivindicaciones, Números

1 – 15 tal como se presentaron inicialmente

Reivindicaciones, Páginas

311-326 tal como se presentaron inicialmente

☐ una lista de secuencias y/o tabla(s) relativa(s) – ver Recuadro Suplementario relativo a Listas de Secuencias

3. Las modificaciones ha ocasionado la cancelación de:

☐ la descripción, páginas
☐ las reivindicaciones, Nos.
☐ los dibujos, hojas/fig.
☐ la lista de secuencias (especificar):
☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

4. ☐ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más allá de la divulgación de la invención tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70.2(c)).

☐ la descripción, páginas
☐ las reivindicaciones, Nos.
☐ los dibujos, hojas/fig.
☐ la lista de secuencias (especificar):
☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

* Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida".

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Recuadro No. III. Ninguna formulación de pinión sobre la novedad, la actividad inventiva y la aplicación industrial

1. Las preguntas con respecto a si el invento reivindicado parece ser novedoso, implica una actividad inventiva (no ser evidente), o ser susceptible de aplicación industrial, por lo que respecta.

☐ al conjunto de la solicitud internacional,
☒ a las reivindicaciones Nos. 1-2, 5, 8-14 (parcialmente todas)

debido a que:

☒ la solicitud internacional, o las reivindicaciones Nos. 9 (con respecto a la aplicación industrial) en cuestión se refieren al objeto, respecto del cual no requiere examen preliminar internacional (especifique):

Ver hoja separada

☐ a descripción, reivindicaciones, o los dibujos (indíquese cuales a continuación) o tales reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa (especifique):

☐ las reivindicaciones, o las reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa.

☒ no se ha emitido informe de búsqueda internacional para dichas reivindicaciones Nos. 1-2, 5, 8-14 (parcialmente todas)

☐ la lista de de secuencias nucleótidas y/o de aminoácidos no cumplen la norma estándar prevista en el Anexo C de las Instrucciones Administrativas por que:

La lista en papel
☐ no se presentó
☐ no cumple con la norma estándar

La lista en formato legible por ordenador
☐ no se presentó
☐ no cumple con la norma estándar

☐ las tablas relativas a las listas de secuencias de nucleótidas y/o de aminoácidos, si únicamente se han presentado en formato legible por ordenador, no cumplen con los

requisitos técnicos previstos en el Anexo C-*bis* de las Instrucciones Administrativas.

☐ Ver recuadro suplementario para más detalles.

Recuadro No. IV Falta de unidad de Invención

1. ☐ En respuesta al requerimiento para limitar las reivindicaciones o pagar tasas adicionales, el solicitante:

   ☐ ha limitado las reivindicaciones
   ☐ ha pagado tasas adicionales
   ☐ ha pagado tasas adicionales bajo protesta
   ☐ no ha limitado las reivindicaciones ni pagado las tasas adicionales.

2. ☒ Esta Administración considera que no se cumple la exigencia de unidad de la invención por los motivos indicados a continuación, y con forme a la Regla 68.1, decide no requerir al solicitante para limitar las reivindicaciones o pagar tasas adicionales.

3. Esta Administración considera que el requerimiento de unidad de invención según las reglas 13.1, 13.2 y 13.3:

   ☐ se cumple
   ☒ no se cumple por las siguientes razones:

4. En consecuencia, el presente informe se ha establecido con relación a las partes siguientes de la solicitud internacional:

   ☒ todas las partes de la solicitud

   ☐ las partes relativas a la reivindicaciones Nos.

Recuadro No. V Declaración razonada según el Artículo 35(2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Si:	Reivindicaciones 3-4, 6-8, 11-15
	No:	Reivindicaciones 1, 2, 5, 9, 10
Nivel Inventivo (NI)	Si:	Reivindicaciones
	No:	Reivindicaciones 1-15

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Aplicación Industrial (AI) Si: Reivindicaciones 1-8, 10-15
No: Reivindicaciones

2. Citas y explicaciones (Regla 70.7)

ver hoja adjunta.

REPORTE DE EXAMEN PRELIMINAR INTERNACI NAL – HOJA ANEXA
Solicitud Internacional No. PCT/IB2004/000836

Re Sección III
No se establece opinión con respecto a novedad, nivel inventivo y aplicación industrial

Las reivindicaciones 1, 2 y 5 abarcan muchos compuestos conocidos que es imposible citar todos los documentos relevantes a la novedad de estas reivindicaciones. Por consiguiente la búsqueda se ha limitado a:

- compuestos de la reivindicación 2 en donde los sustituyentes Y y R3 son como se definen en la reivindicación 3,
- compuestos de la reivindicación 5 en donde los sustituyentes Y y R3 son como se definen en la reivindicación 6, y
- compuestos de la reivindicación 15.

i.e. solo para las reivindicaciones 3-4, 7-8 y 15 se ha realizado una búsqueda completamente.

En la búsqueda:

- la definición de "C3 es carbono" se ha entendido como "C3 es un CH ó un grupo CH2" (i.e. la posición es insustituidos) y
- la definición "anillos completamente insaturados" (e.g. por R2 ó V)se ha entendido como "anillos aromáticos",

que está en línea con los ejemplos.

La reivindicación 9 se relaciona con materia considerada por esta Autoridad cubierta por las provisiones establecidas en la Regla 67.1 (iv) del PCT. Por lo tanto, no se formulará ninguna opinión con respecto a la aplicación industrial de la materia de esta reivindicación (Artículo 34(4)(a)(i) del PCT).

Re Sección IV
Falta de unidad de invención

La presente solicitud carece de unidad de invención de acuerdo con la Regla 13.1 del PCT (ver capítulo II-7 Guía del PCT), puesto que diversos grupos separados de invenciones son reivindicados, que no son unidos por un solo concepto general inventivo.

Estos grupos son:

1 compuestos de la reivindicación 1 en donde C4a en R3 es un átomo de carbono y los compuestos de la reivindicación 15 en donde R11 es CO-R

2 compuestos de la reivindicación 1 en donde C4a en R3 es remplazado por oxigeno o azufre y los compuestos de la reivindicación 15 en donde R11 es hidroxi
3 compuestos de la reivindicación 1 en donde C4a en R3 es reemplazado por nitrógeno
4 compuestos de la reivindicación15 en donde R11 es halo

El problema de la invención era la disposición de un nuevo inhibidor para el tratamiento de arterosclerosis y/o obesidad.

Desde entonces los compuestos de la reivindicación 1 que solucionan el problema de la invención son ya conocidos e.g. D1 y D2, la presente solicitud cae aparte en diferentes grupos de la invención, que no están unidos a un solo concepto general inventivo.

1 los compuestos de la invención 1 difieren de los compuestos del arte previo en que el grupo amino en posición 4 ha sido reemplazado por un sustituyente de carbono opcional,
2 los compuestos de la invención 2 difieren de los compuestos del arte previo en que el grupo amino en posición 4 ha sido reemplazado por un sustituyente de oxigeno o azufre opcional,
3 compuestos de la invención 3 han sido sustancialmente divulgados en el arte previo. Nuevos compuestos de la invención pueden diferir del los compuestos del arte previo e.g. en la opción de un sustituyente específico para una posición especifica,
4 El compuesto de la invención 4 difiere de los compuestos del arte previo en que el grupo amino en posición 4 ha sido reemplazado por un halo.

Entre estos grupos no hay una estructura común que define una contribución sobre el arte previo (característica técnica especial, Regla 13.2 PCT).

La autoridad de búsqueda internacional ha elegido no invitar al solicitante a pagar honorarios adicionales, puesto que la búsqueda tuvo que ser limitada de todas formas a un desbordamiento de los documentos relevantes de la novedad (ver sección III). Se observa sin embargo que la carencia de unidad de invención podría llegar a ser más relevante posteriormente.

Re Sección V
Declaración razonada con respecto a novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración.

Los siguientes artes previos fueron citados en el reporte de búsqueda Internacional:

D1: WO 01/40190 A (PFIZER PROD INC (US)) 7 de Junio de 2001 (2001-06-07)

D2: WO 00/17165 A (PFIZER PROD INC (US)) 30 de Marzo de 2000 (2000-03-30)

D3: WO 96/19458 A (LIGAND PHARM INC) 27 de Junio de 1996 (1996-06-27)

D4: EDWARDS ET AL: BIOORG. MED. CHEM. LETT., vol. 9, No. 7, 1999 páginas 1003-1008, XP002285105

D5: MASSACRET ET AL: EUR. J. ORG. CHEM., vol. 1, 1999, páginas 129-134, XP002285106

D6: Base de Datos CHEMABS [en linea] CHEMICAL ABSTRACT SERVICE, COLUMBUS, OHIO, US; 1992, RUSSELL, JAMES R. ET AL: "Modelo de estudios relacionado con el cofactor de oxomolibdoencimas. Parte 4. Reducción del anillo de pirazina en quinoxalinas y pteridinas" XP002285108 recuperado de la Base de Datos STN acceso No. 1992:490239

D7: BUNCE ET AL: J. ORG CHEM.,vol 66, No. 8, 2001, páginas 2822-2827, XP002285107

D8: DE 351 464 C (CHEMISCHE WERKE GRENZACH AG (D)) 7 de abril de 1922 (1922-04-07)

Novedad (Artículo 33(2) PCT)

D1-D8 divulga compuestos que están abarcados por las presentes reivindicaciones 1, 2 y/o 5. Las presentes reivindicaciones 1, 2, 5, 9 y 10 por lo tanto carecen de novedad.

Nivel Inventivo (Artículo 33(3) del PCT)

D1 y D2 divulga inhibidores CETP. D1 puede ser visto como el más cercano al arte previo.

El problema de la presente invención era la disposición de nuevos inhibidores CETP para el tratamiento de arteroscleroses y/o obesidad.

Entonces la presente invención abarca los ejemplos de D1 y D2, estos no se basan en un nivel inventivo.

La carencia de claridad (Artículo 6 PCT)

Las definiciones de "C3 es carbono", "anillo completamente insaturado" (e.g. para R2 ó V) son ambiguos (ver solo Tema III).

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LUMB, J. Trevor
PFIZER INC.
c/o Jackie Lawrence
Eastern Point Road,
Mailstop 8260-1615
Groton, Connecticut 06340
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

	Date of mailing (day/month/year) 15.02.2005
Applicant's or agent's file reference PC25623A	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IB2004/000836	15.03.2004	28.03.2003

Applicant
PFIZER PRODUCTS INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel. +49 89 2399-8012

Form PCT/IPEA/416 (January 2004)

401

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

402

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC25623A	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IB2004/000836	International filing date *(day/month/year)* 15.03.2004	Priority date *(day/month/year)* 28.03.2003

International Patent Classification (IPC) or national classification and IPC

C07D215/14, C07D215/50, C07D215/12, C07D241/42, C07D401/04, C07D401/12, C07D409/12, C07D405/12, C07D413/12, C07D417/12, C07D403/06, C07D401/06, C07D413/06, C07D405/06, C07D417/06, C07D409/06, A61K31/47, A61K31/4709, A61K31/517, A61P9/10, A61P3/04, A61P3/10

Applicant

PFIZER PRODUCTS INC. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.05.2004	15.02.2005

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Cortés, J Telephone No. +49 89 2399-8206

A03 409

INTERNATIONAL PRELIMINARY REPORT N PATENTABILITY

International application No. PCT/IB2004/000836

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-310 as originally filed

   Claims, Numbers

   1-15 as originally filed

   Claims, Pages

   311-326 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/000836

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-2, 5, 8-14 (all partly)

because:

☒ the said international application, or the said claims Nos. 9 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-2, 5, 8-14 (all partly)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

AOS 4604

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/000836

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-4, 6-8, 11-15
	No:	Claims	1,2,5,9,10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-8, 10-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The claims 1, 2 and 5 encompass so many known compounds that it is impossible to cite all documents relevant to the novelty of these claims. Therefore the search has been limited to:

- compounds of claim 2 wherein the substituents Y and R3 are defined as in claim 3,
- compounds of claim 5 wherein the substituents Y and R3 are defined as in claim 6 and
- compounds of claim 15.

I.e. only the claims 3-4, 7-8 and 15 have been searched completely.

In the search:

- the definition of "C3 is carbon" has been understood as "C3 is a CH or a CH2 group" (i.e. the position is unsubstituted) and
- the definition "fully unsaturated ring" (e.g. for R2 or V) has been understood as "aromatic ring",

which is in line with the examples.

Claim 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated for the industrial applicability of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

The present application lacks unity of invention according to Rule 13.1 PCT (see also chapter III-7 PCT Guidelines), since different separate groups of inventions are claimed which are not linked by a single general inventive concept.

These groups are:

1 compounds of claim 1 wherein C4a in R3 is a carbon atom and compounds of claim 15 wherein R11 is CO-R
2 compounds of claim 1 wherein C4a in R3 is replaced by oxygen or sulphur and compounds of claim 15 wherein R11 is hydroxy
3 compounds of claim 1 wherein C4a in R3 is replaced by nitrogen
4 compounds of claim 15 wherein R11 is halo

The problem of the invention was the provision of new CETP inhibitors for the treatment of artherosclerosis and/or obesity.

Since compounds of claim 1 which solve the problem of the invention are already known from e.g. D1 and D2, the present application falls apart into different groups of invention, which are not linked by a single general inventive concept.

1 The compounds of invention 1 differ from the prior art compounds in that the amino group in 4-position has been replaced by an optionally substituted carbon,

2 The compounds of invention 2 differ from the prior art compounds in that the amino group in 4-position has been replaced by an optionally substituted oxygen or sulphur,

3 Compounds of invention 3 have been substantially disclosed in the prior art. New compounds of invention 3 could differ from the prior art compounds e.g. in the choice of a specific substituent for a specific position,

4 The compounds of invention 4 differ from the prior art compounds in that the amino group in 4-position has been replaced by a halo.

Amongst these groups there is no common structural feature which defines a contribution over the prior art (special technical feature, Rule 13.2 PCT).

The International Searching Authority has chosen not to invite the Applicant to pay additional fees, since the search had to be limited anyway due to an overflow of novelty relevant documents (see item III). It is noted however, that the lack of unity of invention could become relevant at a later stage.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following prior art has been cited in the International Search Report:

D1: WO 01/40190 A (PFIZER PROD INC (US)) 7 June 2001 (2001-06-07)

D2: WO 00/17165 A (PFIZER PROD INC (US)) 30 March 2000 (2000-03-30)

D3: WO 96/19458 A (LIGAND PHARM INC) 27 June 1996 (1996-06-27)

D4: EDWARDS ET AL: BIOORG. MED. CHEM. LETT., vol. 9, no. 7, 1999, pages 1003-1008, XP002285105

D5: MASSACRET ET AL: EUR. J. ORG. CHEM., vol. 1, 1999, pages 129-134, XP002285106

D6: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1992, RUSSELL, JAMES R. ET AL: "Model studies related to the cofactor of oxomolybdoenzymes. Part 4. Reduction of the pyrazine ring in quinoxalines and pteridines" XP002285108 retrieved from STN Database accession no. 1992:490239

D7: BUNCE ET AL: J. ORG CHEM., vol. 66, no. 8, 2001, pages 2822-2827, XP002285107

D8: DE 351 464 C (CHEMISCHE WERKE GRENZACH AG (D)) 7 April 1922 (1922-04-07)

Novelty (Article 33(2) PCT)

D1-D8 disclose compounds which are encompassed by the present claims 1, 2 and/or 5. The present claims 1, 2, 5, 9 and 10 are therefore not novel.

Inventive Step (Article 33(3) PCT)

D1 and D2 disclose CETP inhibitors. D1 can be regarded as the closest prior art.

The problem of the invention was the provision of new CETP inhibitors for the treatment of artherosclerosis and/or obesity.

Since the present application encompasses the examples of D1 and D2, it is not based on an inventive step.

Lack of clarity (Article 6 PCT)

The definitions of "C3 is carbon", "fully unsaturated ring" (e.g. for R2 or V) are ambiguous (see also item III).

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

LUMB, Trevor, J.
c/o LAWRENCE, Jackie
Pfizer Inc.
Mailstop 8260-1615
Eastern Point Road
Groton, CT 06340
United States of America

Date of mailing (day/month/year) 04 November 2004 (04.11.2004)	
Applicant's or agent's file reference PC25623A	IMPORTANT NOTIFICATION
International application No. PCT/IB2004/000836	International filing date (day/month/year) 15 March 2004 (15.03.2004)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
POLLASTRI, Michael, P. 45-2 Chestnut Street Waltham, MA 02453 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

The person indicated in Box 2 should be added to the record as applicant for the US only and inventor for all designated States.

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Fabienne SOCIÉ
Facsimile No. (41-22) 338.70.60	Telephone No. (41-22) 338 9175

411 410

INTERNATI NAL SEARCH REPORT

International application No
PCT/IB2004/000836

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/14 C07D215/50 C07D215/12 C07D241/42 C07D401/04
C07D401/12 C07D409/12 C07D405/12 C07D413/12 C07D417/12
C07D403/06 C07D401/06 C07D413/06 C07D405/06 C07D417/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/40190 A (PFIZER PROD INC (US)) 7 June 2001 (2001-06-07) the whole document	1-15
X	WO 00/17165 A (PFIZER PROD INC (US)) 30 March 2000 (2000-03-30) the whole document	1-15
X	WO 96/19458 A (LIGAND PHARM INC) 27 June 1996 (1996-06-27) page 30, line 30 page 31, line 3 e.g. 1-tert-butoxycarbonyl-4-ethyl-1,2,3,4 tetrahydro-7-methoxy-2-methylquinoline page 302, line 18; example 340 e.g. claim 47, formula (IV)	1,2,9,10

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2004	19/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cortés, J

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2004/000836

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EDWARDS ET AL: BIOORG. MED. CHEM. LETT., vol. 9, no. 7, 1999, pages 1003-1008, XP002285105 compounds of formula 15, page 1005	1,2
X	MASSACRET ET AL: EUR. J. ORG. CHEM., vol. 1, 1999, pages 129-134, XP002285106 compound 3e,3d, 3f, page 129	1,5
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1992, RUSSELL, JAMES R. ET AL: "Model studies related to the cofactor of oxomolybdoenzymes. Part 4. Reduction of the pyrazine ring in quinoxalines and pteridines" XP002285108 retrieved from STN Database accession no. 1992:490239 abstract & JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1: ORGANIC AND BIO-ORGANIC CHEMISTRY (1972-1999) , (10), 1245-9 CODEN: JCPRB4; ISSN: 0300-922X, 1992,	1,5
X	BUNCE ET AL: J. ORG CHEM., vol. 66, no. 8, 2001, pages 2822-2827, XP002285107 compounds 4a-d, scheme 2, page 2823	1
X	DE 351 464 C (CHEMISCHE WERKE GRENZACH AG (D)) 7 April 1922 (1922-04-07) example 4	1

912 4/11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/000836

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2004/000836

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0140190 A	07-06-2001	AU 1048801 A	12-06-2001
		BG 106854 A	29-12-2002
		BR 0015836 A	06-08-2002
		CA 2392979 A1	07-06-2001
		CN 1402711 T	12-03-2003
		EE 200200277 A	15-10-2003
		EP 1246804 A1	09-10-2002
		HU 0203521 A2	28-02-2003
		WO 0140190 A1	07-06-2001
		JP 2003515592 T	07-05-2003
		NO 20022558 A	29-05-2002
		TR 200201446 T2	21-11-2002
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		AU 747715 B2	23-05-2002
		AU 5440399 A	10-04-2000
		BG 105429 A	31-12-2001
		BR 9913855 A	24-07-2001
		CA 2344248 A1	30-03-2000
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		ID 27838 A	26-04-2001
		JP 2002526476 T	20-08-2002
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		SK 3532001 A3	03-12-2001
		TR 200100780 T2	23-07-2001
		TW 502022 B	11-09-2002
		US 6140343 A	31-10-2000
		US 6489478 B1	03-12-2002
		ZA 200101745 A	02-05-2002
WO 9619458 A	27-06-1996	US 5688810 A	18-11-1997
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		BR 9510486 A	02-06-1998
		CA 2208347 A1	27-06-1996
		CN 1175247 A	04-03-1998
		CZ 9701761 A3	16-09-1998
		DE 69531998 D1	27-11-2003
		DK 800519 T3	01-03-2004
		EP 1043325 A1	11-10-2000
		EP 1043326 A1	11-10-2000
		EP 1041071 A1	04-10-2000
		EP 1041066 A1	04-10-2000

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2004/000836

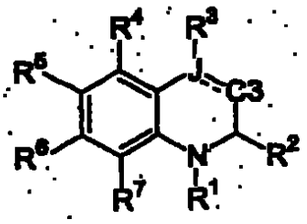
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9619458 A		EP 1043315 A1	11-10-2000
		EP 1382597 A2	21-01-2004
		EP 0800519 A1	15-10-1997
		HU 78117 A2	29-11-1999
		JP 10510840 T	20-10-1998
		NO 972591 A	14-08-1997
		NO 20003534 A	14-08-1997
		NO 20003550 A	14-08-1997
		NO 20003551 A	14-08-1997
		NO 20003552 A	14-08-1997
		NZ 300739 A	26-05-2000
		PT 800519 T	31-03-2004
		RU 2191774 C2	27-10-2002
		WO 9619458 A2	27-06-1996
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		US 5994544 A	30-11-1999
		US 6121450 A	19-09-2000
		US 6448405 B1	10-09-2002
		US 6696459 B1	24-02-2004
DE 351464 C	07-04-1922	NONE	

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

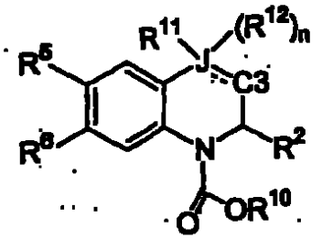
Quinoline and quinoxaline compounds of formulae I or III

wherein the subtituents are as defined in claims 1 and 15

, pharmaceutical compositions containing such compounds and the use of such compounds to elevate certain plasma lipid levels, including high density lipoprotein-cholesterol and to lower certain other plasma lipid levels, such as LDL-cholesterol and triglycerides and accordingly to treat diseases which are exacerbated by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in some mammals, including humans.



Formula I



Formula III

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/000836

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

414
415

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05896777 00000000 Folios: 413
Fecha (AMD): 2005-09-23 17:30:58
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN / **MODELO DE UTILIDAD**	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( )	**INCOMPLETA**	( ) ( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	**INCOMPLETA**	( ) ( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( )	**INCOMPLETA**	( ) ( )

Firma Responsable:

Fecha: 23 de 2005

415
416

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
PFIZER PRODUCTS INC

REFERENCIA	Radicación No.	5 96777
	Solicitud internacional	IB2004/000836
	Fecha inicio fase nacional	28/10/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	11702

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 DIC. 2005
adpa1