



PCT

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTAR

10-54279

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE
INVENCION

TITULO: DERIVADOS DE 1, 2, -TRIAZOL PARA USO COMO
INHIBIDORES DE ESTEAROIL-COENZIMA A DESATURASA

SOLICITANTE: GLAXOSMITHKLINE LLC

DIRECCIÓN: One Franklin, Plaza, 200 North 16th Street Philadelphia,
Pennsylvania 19102, Estados Unidos

APODERADO: CARLOS R. OLARTE

BOGOTÁ 6 de Mayo de 2010

P2010/000050

Edi, Cova, Arthur Sillerbach
09-06-2010
vo Ecu

OLARTE RAISBECK

OLARTE RAISBECK MOUR

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-054279- -00000-0000

Fecha: 2010-05-06 16:40:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 289



PETITORIO - FORMULARIO

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2010/000050

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)

Nombre: GLAXOSMITHKLINE LLC

Dirección: One Franklin Plaza, 200 North 16th
Street Philadelphia, Pennsylvania 19102

Nacionalidad o Domicilio: Estadounidense

Lugar de Constitución: Estados Unidos de
América.

Teléfono: _____ Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

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Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79782747Bta
TP 74.295

INVENTOR (ES)
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Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/EP2008/065104 Fecha Noviembre 7, 2008

Publicación Internacional No. WO 2009/060053 Fecha Mayo 14, 2009

6

Título (54) DERIVADOS DE 1, 2, 3-TRIAZOL PARA USO COMO INHIBIDORES DE
ESTEAROIL-COENZIMA A DESATURASA

Clasificación Internacional (51) C07D 249/04, C07D 413/12, A61K 31/4192,
A61P 3/06

Prioridad

SI ☒ NO ☐

(33) País de Origen

GB

(32) Fecha

Noviembre 9, 2007

(31) Número de Solicitud

0722077.5

9

Comprobante de pago No. 10-

Fecha Mayo 6, 2010



ANEXOS



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.



Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 09-149.371



Documento de cesión del inventor al solicitante o a su causante. Declaración bajo la Regla 4.176(i) PCT.
Declaraciones.



Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).



Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).



Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).



Traducción del examen preliminar internacional efectuado por la IPEA.



De ser el caso, copia del contrato de acceso.



De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.



De ser el caso, certificado de depósito del material biológico.



Arte final 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.



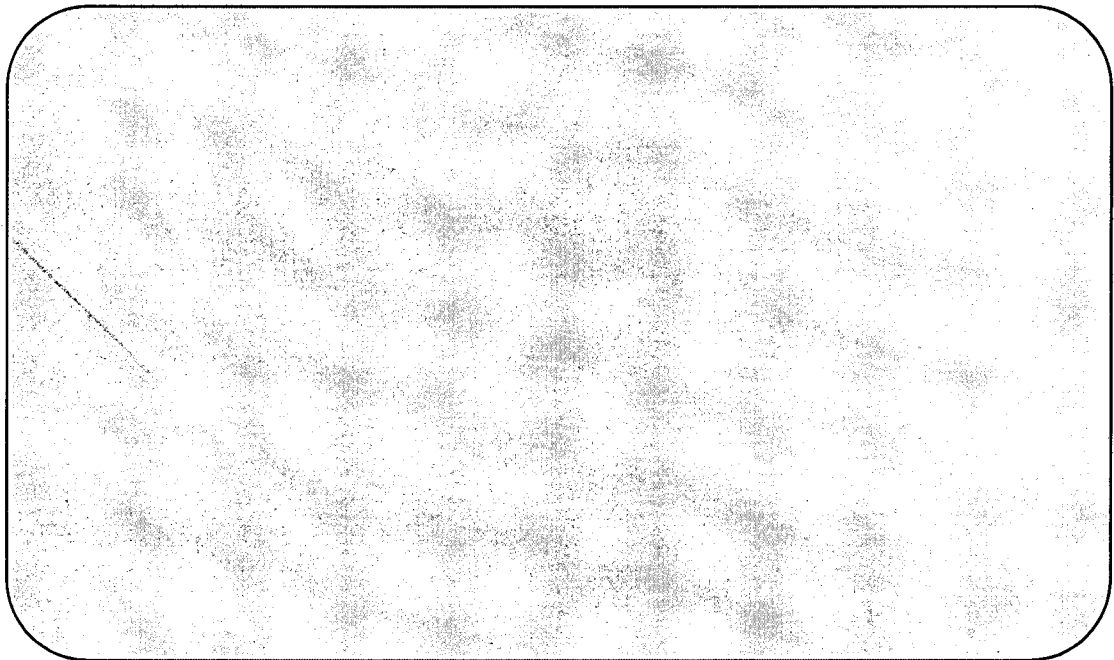
De ser el caso, modificaciones efectuadas a la solicitud internacional.



Otros. Búsqueda Internacional



FIGURA CARACTERÍSTICA:



Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Bta T.P. 74.295

LISTA DE INVENTORES

PCT/EP2008/065104

3

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 35,517

FECHA : MAYO 5 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-054279- -00000-0000

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 Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
 Act. 411 PRESENTACION Folios: 289

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	6238665	05/05/2010	4,158,000.00
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	174686676	05/05/2010	706,000.00
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	174686680	05/05/2010	1,412,000.00
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	174695205	05/05/2010	706,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554,000.00
		TOTAL :	\$ 554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Apostilla adjunta:

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

1. País: Estados Unidos de América
El presente documento público
2. Ha sido firmado por: Deborah A. Becker
3. Actuando en calidad de: Notario Público
Deborah A. Becker, Notario Público del
4. Lleva el sellò/estampilla de: Condado de Montgomery, Mancomunidad de Pensilvania.
- Certificado
5. En: Harrisburg, Pensilvania.
6. El: Día 9 de febrero de 2010
7. Por: Pedro A. Cortés, Secretario de la Mancomunidad de Pensilvania.
8. Bajo el No.: 201003472
9. Sello / estampilla: Gran sello del Secretario de la Mancomunidad de Pensilvania.
10. Firma: Por: (Firmado) Pedro A. Cortés

"FIN DE LA TRADUCCIÓN"

Certificación:

Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.

Documento: "Apostilla"

Fecha: 25 de febrero de 2010.

Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)

Licencia # 376 de 1993, expedida por el Ministerio de Justicia.

Dirección: Carrera 15 # 99-18 Of. 411, Bogotá, D.C.

Teléfonos: (571) 218 2308, (571) 623 2925.

E-mail: twacoe1@yahoo.com

Traducción # 14-618

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376-1993 Ministerio de Justicia

6

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

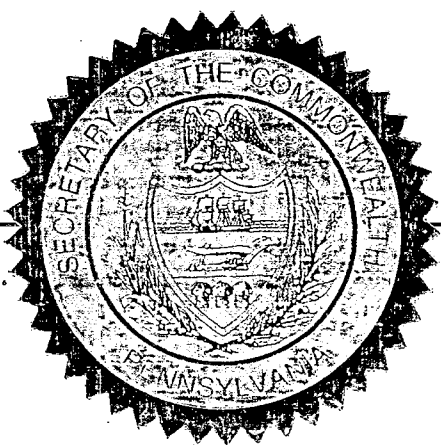
1. Country : United States of America
2. This public document has been signed by **DEBORAH A BECKER**
3. acting in the capacity of **NOTARY PUBLIC**
4. bears the seal/stamp **DEBORAH A BECKER , NOTARY PUBLIC, MONTGOMERY COUNTY, COMMONWEALTH OF PENNSYLVANIA**

Certified

5. at Harrisburg, Pennsylvania
6. The 9th day of February, 2010
7. by Pedro A. Cortés, Secretary of the Commonwealth of Pennsylvania
8. No: 201003472
9. Seal/Stamp
10. Signature

Pedro A. Cortés

Pedro A. Cortés



Power of Attorney

The undersigned,

domiciled in

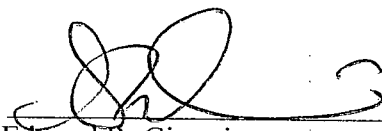
One Franklin Plaza, 200 North 16th Street Philadelphia, Pennsylvania 19102
by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right 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, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. 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.

El suscrito,
GLAXOSMITHKLINE LLC

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro** poder amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual 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, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, 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 motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:


Edward R. Gimmi

Date/Fecha: 18 January 2010

City/Country/Ciudad,País: King of Prussia, Pennsylvania, USA

Poder

Carlos R. Olarte
J. Ian Raisbeck
Juan Guillermo Moure
Natalia Castro
Alexander Agudelo
Catalina Barbastefano
Ángela Correa
Erika Rico
Carlos A. Parra
Andrés Alvarado
Gina Arias
Juan Felipe Acosta
Andrés Rincón
Grace Garcia
Mariana Franco

Of Counsel
Guillermo Chahín
Graciela Melo
Jacqueline Chaparro

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

Certificación Notarial

On this date,
18 January 2010

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

709 Swedeland Road, King of Prussia, Pennsylvania, USA
signed the foregoing document.

2. That the grantor has executed the foregoing
document as Authorized Attorney and
Signatory
of GlaxoSmithKline LLC

3. That GlaxoSmithKline LLC,
having its principal place of business located in
Philadelphia, Pennsylvania, USA
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):

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Edward R. Gimmi
mayor de edad y domiciliado
suscribió el documento que antecede.

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

3. 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
suscibir 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):

NOTARY PUBLIC (Signature)

COMMONWEALTH OF PENNSYLVANIA

Notarial Seal
Deborah A. Becker, Notary Public
Upper Merion Twp., Montgomery County
My Commission Expires April 6, 2012
Member, Pennsylvania Association of Notaries

Box No. VIII(ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general and the specific Notes to Box No. VIII(ii)). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

SMITHKLINE BEECHAM CORPORATION is entitled to apply for and be granted a patent by virtue of the following:

- (i) transfer of entitlement from inventors Anne Marie Jeanne BOUILLOT, Alain LAROZE and Lionel TROTET to Laboratoire GlaxoSmithKline S.A.S. by way of employment contract
- (ii) an assignment from Laboratoire GlaxoSmithKline S.A.S. to SmithKline Beecham Corporation dated 8 October 2008

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII(ii)".

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 May 2009 (14.05.2009)

PCT

(10) International Publication Number
WO 2009/060053 A1

(51) International Patent Classification:

C07D 249/04 (2006.01) A61K 31/4192 (2006.01)
C07D 413/12 (2006.01) A61P 3/06 (2006.01)

(74) Agents: REED, Michael A. et al.; GlaxoSmithKline, Corporate Intellectual Property, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(21) International Application Number:

PCT/EP2008/065104

(22) International Filing Date:

7 November 2008 (07.11.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0722077.5 9 November 2007 (09.11.2007) GB

(71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM CORPORATION
[US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BOUILLOT, Anne, Marie, Jeanne [FR/FR]; Laboratoire GlaxoSmithKline, Centre de Recherches, Z.A. de Courtaboeuf, 25 avenue du Québec, F-91940 Les Ulis (FR). LAROZE, Alain [FR/FR]; Laboratoire GlaxoSmithKline, Centre de Recherches, Z.A. de Courtaboeuf, 25 avenue du Québec, F-91940 Les Ulis (FR). TROTTET, Lionel [FR/FR]; Laboratoire GlaxoSmithKline, Centre de Recherches, Z.A. de Courtaboeuf, 25 avenue du Québec, F-91940 Les Ulis (FR).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

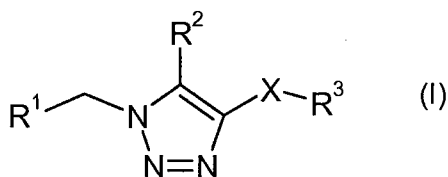
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report

(54) Title: 1, 2, 3-TRIAZOLE DERIVATIVES FOR USE AS STEAROYL-COA DESATURASE INHIBITORS



(57) Abstract: The present invention relates to substituted triazole compounds of the formula (I) and pharmaceutically acceptable salts thereof, to pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to compounds for modulating SCD activity.

1, 2, 3-TRIAZOLE DERIVATIVES FOR USE AS STEAROYL-COA DESATURASE INHIBITORS

COMPOUNDSFIELD OF THE INVENTION

5 The present invention relates to a novel class of compounds believed to be inhibitors of stearoyl-CoA desaturase (SCD), compositions comprising said compounds, methods of synthesis and uses for such compounds in treating and/or preventing various diseases, including those mediated by SCD enzyme, such as diseases related to elevated lipid levels, cardiovascular disease, diabetes, obesity, metabolic syndrome, skin disorders
10 such as acne, diseases or conditions related to cancer and the treatment of symptoms linked to the production of the amyloid plaque-forming A β 42 peptide such as Alzheimer's disease and the like.

BACKGROUND OF THE INVENTION

15 Acyl desaturase enzymes catalyze the formation of double bonds in fatty acids derived from either dietary sources or *de novo* synthesis in the liver. Mammals synthesise at least three fatty acid desaturases of differing chain length that specifically catalyze the addition of double bonds at the delta-9, delta-6, and delta-5 positions. Stearoyl-CoA desaturases (SCDs) introduce a double bond in the C9-C10 position of saturated fatty acids. The
20 preferred substrates for the enzymes are palmitoyl-CoA (16:0) and stearoyl-CoA (18:0), which are converted to palmitoleoyl-CoA (16:1) and oleoyl-CoA (18:1), respectively. The resulting mono-unsaturated fatty acids may then be employed in the preparation of phospholipids, triglycerides, and cholesteryl esters, *in vivo*.

25 A number of mammalian SCD genes have been cloned. For example, two genes have been cloned from rats (SCD1, SCD2) and four SCD genes have been isolated from mice (SCD1, 2, 3 and 4). While the basic biochemical roles of SCD has been known in rats and mice since the 1970's (Jeffcoat, R *et al.*, *Elsevier Science* (1984), Vol 4, pp. 85-112; de Antueno, RJ, *Lipids* (1993), Vol. 28, No. 4, pp. 285-290), it has only recently been
30 directly implicated in human diseases processes.

A single SCD gene, SCD1, has been characterized in humans. SCD1 is described in Brownlie *et al*, WO 01/62954. A second human SCD isoform has been identified, and
35 because it bears little sequence homology to known mouse or rat isoforms it has been named human SCD5 or hSCD5 (WO 02/26944).

Whilst not wishing to be bound by theory, it is thought that inhibition of the activity of SCD *in vivo* can be used to ameliorate and/or treat one or more diseases such as dyslipidemia,
40 hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia, metabolic syndrome; other cardiovascular diseases

e.g. peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis; hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver.

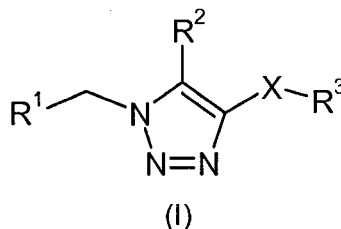
5 An SCD-mediated disease or condition also includes a disorder of polyunsaturated fatty acid (PUFA) disorder, or a skin disorder, including but not limited to eczema, acne, psoriasis, keloid scar formation or prevention, diseases related to production or secretions from mucous membranes, such as monounsaturated fatty acids, wax esters, and the like (US2006/0205713A1, WO2007/046868, WO2007/046867). SCD has been shown to play
10 a physiological role in cholesterol homeostasis and the de novo biosynthesis of cholesterol esters, triglycerides and wax esters required for normal skin and eyelid function and therefore may be useful in the treatment of acne and other skin conditions (Makoto et al. J of Nutrition (2001), 131(9), 2260-2268, Harrison et al. J of Investigative Dermatology (2007) 127(6), 1309-1317).

15 An SCD-mediated disease or condition also includes but is not limited to a disease or condition which is, or is related to cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like (US2006/0205713A1, WO2007/046868, WO2007/046867). Recently, SCD-1 has been identified as playing a
20 role in human tumor cell survival and therefore has potential as an anticancer target (Morgan-Lappe et al. 2007 Cancer Res. 67(9) 4390-4398).

It has been shown that overexpression of Steroyl-CoA desaturase (SCD) in human cells in culture leads to a specific increase in the production of the amyloid plaque-forming A β 42
25 peptide, and conversely, that reductions in SCD activity in human cells in culture leads to a specific decrease in the production of A β 42. Therefore, SCD inhibitors may also be useful for treating, delaying the onset of symptoms, or slowing the progression of symptoms of mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other
30 neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42 (US2007/0087363A1; Myriad Genetics).

WO2005/011657 describes certain piperazine derivatives useful for inhibiting SCD activity.

35 The present invention provides a compound of formula (I) for inhibiting SCD activity:



wherein:

X represents -CONH-, -NHCO- or -CH₂NH-;

5 R¹ represents:

-C₆₋₁₀aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from:

- 10 (a) -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₆haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro);
- (b) phenyl optionally substituted by one, two or three groups independently selected from: halogen (such as chloro, bromo or fluoro);

R² represents hydrogen or -C₁₋₆alkyl (such as -CH₃);

15

R³ represents:

-C₆₋₁₀aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from:

- 20 (a) -C₁₋₆alkyl (such as -CH₃), -C₁₋₆alkenyl, -C₁₋₆alkoxy (such as -OCH₃ or -OC₂H₄CH(CH₃)₂), -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, -C₀₋₆alkylOH (such as -CH₂OH, -C(CH₃)₂OH or -CH(CH₃)OH), -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₆haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro);
- 25 (b) -C₅heteroaryl (such as oxazole);

R⁴ represents -C₆₋₁₀aryl (such as phenyl);

R⁵ represents -H or -C₁₋₆alkyl (such as -CH₃);

R⁶ represents -H or -C₁₋₃alkyl (such as -CH₃) or -C₁₋₃alkylOH;

30 R⁷ represents -H or -C₁₋₃alkyl (such as -CH₃);

R⁸ represents -H or -C₁₋₃alkyl (such as -CH₃);

R⁹ represents -H or -C₁₋₃alkyl (such as -CH₃);

m represents 1-3;

35 n represents 0-3;

p represents 0-3; and

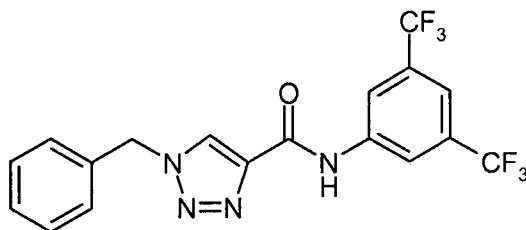
q represents 1-3;

or a pharmaceutically acceptable salt thereof;

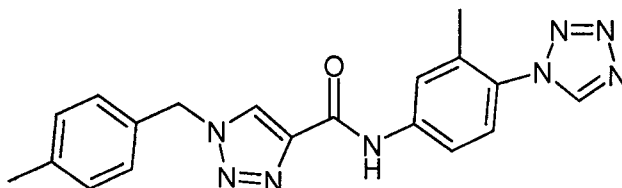
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with the proviso that the compound of formula (I) is not

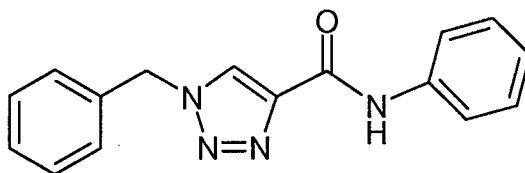
N-[3,5-bis(trifluoromethyl)phenyl]-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,



N-[2-(5-methyl-2-furanyl)phenyl]-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,



or, N-phenyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide.



The said compounds have been found to inhibit SCD activity and may therefore be useful in the treatment of SCD-mediated diseases such as diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; other cardiovascular diseases e.g. peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; skin disorders e.g. eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42.

In one aspect of the invention, X represents -CONH-. In another aspect of the invention, X represents -NHCO-. In another aspect of the invention, X represents -CH₂NH-. In another aspect of the invention, X represents -CONH- or -CH₂NH-.

In one aspect of the invention, R¹ represents phenyl substituted by one, two or three groups independently selected from:

- 5 (a) -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₆haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro),
- (b) phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

10 In another aspect of the invention, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from:

- (a) -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₆haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro),
- 15 (b) phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

20 In another aspect of the invention, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₆haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro).

25 In another aspect of the invention, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₃haloalkyl (such as -CF₃), -OC₁₋₃haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

30 In another aspect of the invention, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂), -OCH₃, -C₁₋₃haloalkyl (such as -CF₃), -OC₁₋₃haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro), or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro).

35 In another aspect of the invention, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂) or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

40 In another aspect of the invention, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₆alkyl (such as -CH₃ or -CH(CH₃)₂) or

halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro).

5 In another aspect of the invention, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂) or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

10 In another aspect of the invention, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -C₁₋₃alkyl (such as -CH₃ or -CH(CH₃)₂) or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro).

15 In another aspect of the invention, R¹ represents phenyl optionally substituted by one, two or three groups independently selected from: -CH₃, -CH(CH₃)₂ or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one, two or three groups selected from: halogen (such as chloro, bromo or fluoro).

20 In another aspect of the invention, R¹ represents phenyl optionally substituted by one or two groups independently selected from: -CH₃, -CH(CH₃)₂ or halogen (such as chloro, bromo or fluoro) or phenyl optionally substituted by one or two groups selected from: halogen (such as chloro, bromo or fluoro).

25 In another aspect of the invention, R¹ represents phenyl substituted by two groups independently selected from halogen (such as chloro, bromo or fluoro).

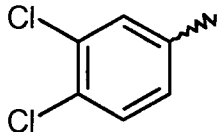
In another aspect of the invention, R¹ represents phenyl substituted by a group independently selected from halogen (such as chloro, bromo or fluoro).

30 In another aspect of the invention, R¹ represents phenyl substituted by phenyl optionally substituted by halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R¹ represents phenyl substituted by phenyl.

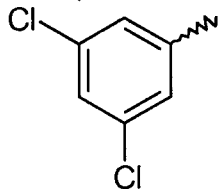
35 In another aspect of the invention, R¹ represents phenyl substituted by two chloro groups.

In another aspect of the invention, R¹ is phenyl substituted in the meta position, that is in the 3 position, and the para position, that is in the 4 position, by halogen e.g chloro i.e.



40

In another aspect of the invention, R^1 is phenyl substituted in the meta position, that is in the 3 position and 5 position, by halogen e.g. chloro i.e.



5 In another aspect of the invention, R^1 is phenyl.

In one aspect of the invention, R^2 represents hydrogen. In another aspect of the invention, R^2 represents $-C_{1-6}$ alkyl. In another aspect of the invention, R^2 represents $-C_{1-3}$ alkyl. In another aspect of the invention, R^2 represents $-CH_3$ (methyl). In another aspect of the invention, R^2 represents hydrogen or $-C_{1-3}$ alkyl.

In one aspect of the invention, R^3 represents phenyl optionally substituted by one, two or three groups independently selected from:

- 15 (a) $-C_{1-6}$ alkyl (such as $-CH_3$), $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-6}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}$ alkylOH, $-C_{1-6}$ haloalkyl (such as $-CF_3$), $-OC_{1-6}$ haloalkyl (such as $-OCF_3$), $-C_{3-6}$ cycloalkyl, $-OC_{3-6}$ cycloalkyl or halogen (such as chloro, bromo or fluoro),
- 20 (b) $-C_5$ heteroaryl (such as oxazole).

In another aspect of the invention, R^3 represents phenyl optionally substituted by one or two groups independently selected from:

- 25 (a) $-C_{1-6}$ alkyl (such as $-CH_3$), $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-6}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}$ alkylOH, $-C_{1-6}$ haloalkyl (such as $-CF_3$), $-OC_{1-6}$ haloalkyl (such as $-OCF_3$), $-C_{3-6}$ cycloalkyl, $-OC_{3-6}$ cycloalkyl or halogen (such as chloro, bromo or fluoro),
- 30 (b) $-C_5$ heteroaryl (such as oxazole).

In another aspect of the invention, R^3 represents phenyl optionally substituted by:

(i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or,

(ii) one, two or three groups independently selected from:

- 35 (a) $-C_{1-6}$ alkyl (such as $-CH_3$), $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-6}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}$ alkylOH, $-C_{1-6}$ haloalkyl (such as $-CF_3$), $-OC_{1-6}$ haloalkyl (such as $-OCF_3$), $-C_{3-6}$ cycloalkyl, $-OC_{3-6}$ cycloalkyl or halogen (such as chloro, bromo or fluoro),
- 40

(b) -C₅heteroaryl (such as oxazole).

In another aspect of the invention, R³ represents phenyl optionally substituted by:

(i) one group independently selected from -(CH₂)_nCO₂R⁵ or -C(=O)NHR⁶ and/or,

5 (ii) one or two groups independently selected from:

(a) -C₁₋₆alkyl (such as -CH₃), -C₁₋₆alkenyl, -C₁₋₆alkoxy (such as -OCH₃ or -OC₂H₄CH(CH₃)₂), -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nOC(=O)R⁵, -C₀₋₆alkylOH (such as -CH₂OH, -C(CH₃)₂OH or -CH(CH₃)OH), -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₆haloalkyl (such as -CF₃), -OC₁₋₆haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro),

(b) -C₅heteroaryl (such as oxazole).

In another aspect of the invention, R³ represents phenyl optionally substituted by:

15 (i) one group independently selected from -(CH₂)_nCO₂R⁵ or -C(=O)NHR⁶ and/or,

(ii) one, two or three groups independently selected from:

(a) -C₁₋₃alkyl (such as -CH₃), -C₁₋₃alkenyl, -C₁₋₆alkoxy (such as -OCH₃ or -OC₂H₄CH(CH₃)₂), -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nOC(=O)R⁵, -C₀₋₃alkylOH (such as -CH₂OH, -C(CH₃)₂OH or -CH(CH₃)OH), -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₃haloalkyl (such as -CF₃), -OC₁₋₃haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro),

(b) -C₅heteroaryl (such as oxazole).

25 In another aspect of the invention, R³ represents phenyl optionally substituted by:

(i) one group independently selected from -(CH₂)_nCO₂R⁵ or -C(=O)NHR⁶ and/or,

(ii) one or two groups independently selected from:

(a) -C₁₋₃alkyl (such as -CH₃), -C₁₋₃alkenyl, -C₁₋₆alkoxy (such as -OCH₃ or -OC₂H₄CH(CH₃)₂), -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nOC(=O)R⁵, -C₀₋₃alkylOH (such as -CH₂OH, -C(CH₃)₂OH or -CH(CH₃)OH), -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₃haloalkyl (such as -CF₃), -OC₁₋₃haloalkyl (such as -OCF₃), -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen (such as chloro, bromo or fluoro),

(b) -C₅heteroaryl (such as oxazole).

35 In another aspect of the invention, R³ represents phenyl optionally substituted by:

(i) one group independently selected from -(CH₂)_nCO₂R⁵ or -C(=O)NHR⁶ and/or,

(ii) one, two or three groups independently selected from:

(a) -C₁₋₃alkyl (such as -CH₃), -C₁₋₃alkenyl, -C₁₋₆alkoxy (such as -OCH₃ or -OC₂H₄CH(CH₃)₂), -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nOC(=O)R⁵, -C₀₋₃alkylOH (such as -CH₂OH, -CH(CH₃)₂OH or -CH(CH₃)OH) -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH or halogen (such as chloro, bromo or fluoro),

(b) -C₅heteroaryl (such as oxazole).

In another aspect of the invention, R^3 represents phenyl optionally substituted by:

(i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or,

(ii) one or two groups independently selected from:

- 5 (a) $-C_{1-3}$ alkyl (such as $-CH_3$), $-C_{1-3}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-3}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}$ alkylOH or halogen (such as chloro, bromo or fluoro),
 (b) $-C_5$ heteroaryl (such as oxazole).

10 In another aspect of the invention, R^3 represents phenyl optionally substituted by:

(i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or,

(ii) one, two or three groups independently selected from:

- 15 (a) $-C_{1-3}$ alkyl (such as $-CH_3$), $-C_{1-3}$ alkenyl, $-C_{1-6}$ alkoxy (such as $-OCH_3$ or $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-3}$ alkylOH (such as $-CH_2OH$, $-C(CH_3)_2OH$ or $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}$ alkylOH or halogen (such as chloro, bromo or fluoro),
 (b) oxazole.

20 In another aspect of the invention, R^3 represents phenyl optionally substituted by:

(i) one group independently selected from $-CO_2H$, $-CO_2CH_3$, $-CO_2C_2H_5$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)NHC_2H_5$ or $-C(=O)NHC_2H_4OH$ and/or,

(ii) one, two or three groups independently selected from:

- 25 (a) $-CH_3$, $-C(=CH_2)CH_3$, $-OCH_3$, $-OC_2H_4CH(CH_3)_2$, $-OCH_2R^4$, $-CH_2OC(=O)R^4$, $-CH_2OC(=O)CH_3$, $-CH_2OH$, $-C_2H_4OH$, $-CH(CH_3)OH$, $-C(CH_3)_2OH$, $-OH$, $-CH_2NHC(=O)CH_3$, $-NHC(=O)CH_3$, $-OC_2H_4N(CH_3)_2$, $-OC_2H_4OH$ or halogen (such as chloro, bromo or fluoro),
 (b) oxazole.

30 In another aspect of the invention, R^3 represents phenyl optionally substituted by:

(i) one group independently selected from $-CO_2H$, $-CO_2CH_3$, $-CO_2C_2H_5$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)NHC_2H_5$ or $-C(=O)NHC_2H_4OH$ and/or,

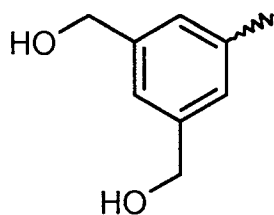
(ii) one or two groups independently selected from:

- 35 (a) $-CH_3$, $-C(=CH_2)CH_3$, $-OCH_3$, $-OC_2H_4CH(CH_3)_2$, $-OCH_2R^4$, $-CH_2OC(=O)R^4$, $-CH_2OC(=O)CH_3$, $-CH_2OH$, $-C_2H_4OH$, $-CH(CH_3)OH$, $-C(CH_3)_2OH$, $-OH$, $-CH_2NHC(=O)CH_3$, $NHC(=O)CH_3$, $-OC_2H_4N(CH_3)_2$, $-OC_2H_4OH$ or halogen (such as chloro, bromo or fluoro),
 (b) oxazole.

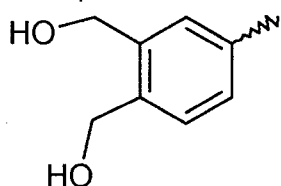
40 In another aspect of the invention, R^3 represents phenyl optionally substituted by one or two $-CH_2OH$ groups.

In another aspect of the invention, R^3 represents phenyl substituted by one or two $-CH_2OH$ groups.

In another aspect of the invention, R^3 is phenyl substituted in the meta position, that is in the 3 and 5 position, by $-CH_2OH$ i.e.



- 5 In another aspect of the invention, R^1 is phenyl substituted in the meta position, that is in the 3 position and the para position, that is in the 4 position, by $-CH_2OH$ i.e.



In another aspect of the invention, R^3 represents phenyl substituted by $-CH_2OH$.

10

In one aspect of the invention, R^4 represents phenyl.

In one aspect of the invention, R^5 represents hydrogen. In another aspect of the invention, R^5 represents $-C_{1-6}$ alkyl. In another aspect of the invention, R^5 represents $-C_{1-3}$ alkyl.

- 15 In another aspect of the invention, R^5 represents $-C_2H_5$ (ethyl). In another aspect of the invention, R^5 represents $-CH_3$ (methyl).

In one aspect of the invention, R^6 represents hydrogen. In another aspect of the invention, R^6 represents $-C_{1-3}$ alkyl. In another aspect of the invention, R^6 represents $-C_2H_5$ (ethyl). In another aspect of the invention, R^6 represents $-CH_3$ (methyl). In another aspect of the invention, R^6 represents $-C_{1-3}$ alkylOH. In another aspect of the invention, R^6 represents $-C_2H_4OH$.

20

In one aspect of the invention, R^7 represents hydrogen. In another aspect of the invention, R^7 represents $-C_{1-3}$ alkyl. In another aspect of the invention, R^7 represents $-CH_3$ (methyl).

25

In one aspect of the invention, R^8 represents hydrogen. In another aspect of the invention, R^8 represents $-C_{1-3}$ alkyl. In another aspect of the invention, R^8 represents $-CH_3$ (methyl).

In one aspect of the invention, R^9 represents hydrogen. In another aspect of the invention, R^9 represents $-C_{1-3}$ alkyl. In another aspect of the invention, R^9 represents $-CH_3$ (methyl).

30

In one aspect of the invention, m represents 1 or 2. In another aspect of the invention, m represents 2. In another aspect of the invention, m represents 1.

35

In one aspect of the invention, n represents 0, 1 or 2. In another aspect of the invention, n represents 3. In another aspect of the invention, n represents 2. In another aspect of the invention, n represents 1. In another aspect of the invention, n represents 0.

5 In one aspect of the invention, p represents 0, 1 or 2. In another aspect of the invention, p represents 2. In another aspect of the invention, p represents 1. In another aspect of the invention, p represents 0.

10 In one aspect of the invention, q represents 1 or 2. In another aspect of the invention, q represents 2. In another aspect of the invention, q represents 1.

Each of the aspects of the invention are independent unless stated otherwise. Nevertheless the skilled person will understand that all the permutations of the aspects of described are within the scope of the invention. Thus it is to be understood that the present invention covers all combinations of suitable, convenient and exemplified groups described herein. For example, in one aspect the invention provides a compound of formula (I) wherein X represents -CONH- and R² represents -CH₃.

20 Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The invention also extends to conformational isomers of compounds of formula (I) and any geometric (*cis* and/or *trans*) isomers of said compounds. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

30 It will be appreciated that racemic compounds of formula (I) may be optionally resolved into their individual enantiomers. Such resolutions may conveniently be accomplished by standard methods known in the art. For example, a racemic compound of formula (I) may be resolved by chiral preparative HPLC.

35 It will also be appreciated that compounds of the invention which exist as polymorphs, and mixtures thereof, are within the scope of the present invention.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl. However, when a moiety is defined such that alkyl bears a substituent it will be clear to the skilled person from the context that alkyl may include alkylene, for example methylene (-CH₂-), ethylene (-CH₂CH₂-) and propylene (-CH₂CH₂CH₂-).

As used herein, the term "alkylOH" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and a hydroxyl group. For example, -C₁₋₆alkylOH means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms and OH.

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In one aspect of the invention, the term "alkylOH" refers to straight hydrocarbon chains containing the specified number of carbon atoms and a hydroxyl group. For example, -C₁₋₆alkylOH means a straight alkyl containing at least 1, and at most 6, carbon atoms and OH. In one aspect of the invention, the alkyl chain in -C₁₋₆alkylOH is a straight hydrocarbon chain containing the specified number of carbon atoms and a hydroxyl group.

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As used herein, the term "alkenyl" refers to straight or branched chain hydrocarbon chains containing the specified number of carbon atoms and one or more double bonds. For example, -C₁₋₆alkenyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms and at least one double bond. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl, 1-methylethenyl, propyl-2-ene, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl or 3-hexenyl.

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As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C₁₋₆alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy and hexyloxy. The point of attachment may be on the oxygen or carbon atom.

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As used herein, the term "halogen" or "halo" refers to a fluorine (fluoro), chlorine (chloro), bromine (bromo) or iodine (iodo) atom.

As used herein, the term "haloalkyl" refers to an alkyl group having one or more carbon atoms and wherein at least one hydrogen atom is replaced with a halogen atom, for example a trifluoromethyl group and the like.

30

As used herein, the term "cycloalkyl" refers to a saturated cyclic group containing 3 to 6 carbon ring-atoms. Examples include cyclopropyl, cyclopentyl and cyclohexyl.

35

As used herein, the term "C₅₋₁₀heteroaryl" refers to an aromatic cyclic group containing 5 to 10 ring-atoms 1, 2, 3 or 4 of which are hetero-atoms independently selected from nitrogen, oxygen and sulphur and the remaining ring-atoms are carbon, e.g. benzothiophenyl, indolyl or thienyl. This definition includes both monocyclic and bicyclic ring systems and bicyclic structures at least a portion of which is aromatic and the other part is saturated, partially or fully unsaturated.

40

As used herein, the term 'aryl' means an aromatic carbocyclic moiety. The definition includes both monocyclic and bicyclic ring systems and bicyclic structures at least a portion of which is aromatic and the other part is saturated, partially or fully unsaturated. Examples of aromatic, aryl groups include naphthyl, anthryl, phenanthryl, indanyl, indenyl, azulenyl, azulanyl, fluorenyl, phenyl and naphthyl, and more specifically phenyl.

Examples of heteroaryl groups include: furyl, thienyl, pyrrolyl, pyrrolinyl, imidazolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, sulfolanyl, tetrazolyl, triazinyl, azepinyl, oxazepinyl, thiazepinyl, diazepinyl and thiazolinyl, benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, benzothiophenyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl.

In one aspect of the invention, -C₅heteroaryl is a 5 membered aromatic cyclic group containing 5 ring-atoms 1, 2 or 3 of which are hetero-atoms independently selected from nitrogen, oxygen and sulphur and the remaining ring-atoms are carbon, e.g. oxazole.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated. For the avoidance of doubt, the term "independently" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

Salts of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion is pharmaceutically acceptable. However, salts having non-pharmaceutically acceptable counterions are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, malic, mandelic, acetic, fumaric, glutamic, lactic, citric, tartaric, benzoic, benzenesulfonic, *p*-toluenesulfonic, methanesulfonic, ethanesulfonic or naphthalenesulfonic acid. Other non-pharmaceutically acceptable salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Reference is made to Berge et al. J. Pharm. Sci., 1977, 66, 1-19.

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms thereof.

- 5 Solvates of the compounds of formula (I) and solvates of the salts of the compounds of formula (I) are included within the scope of the present invention.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. In one aspect of the invention, the solvent used is a pharmaceutically acceptable solvent. In another aspect of the invention, the solvent used is water and the solvate may also be referred to as a hydrate.

- 15 Solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the solvent is pharmaceutically acceptable. However, solvates having non-pharmaceutically acceptable solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts.

Prodrugs of the compounds of formula (I) are included within the scope of the present invention.

- 25 As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987 and in D. Fleishner, S. Ramon and H. Barba "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved in vivo yielding the parent compound. Prodrugs may include, for example, compounds of this invention wherein hydroxyl or amine groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy or amine groups. Thus, representative examples of prodrugs include (but are not limited to) phosphonate, carbamate, acetate, formate and benzoate derivatives of hydroxy and amine functional groups of the compounds of formula (I).

Phosphonates, acetates, benzoates and carbamates may be active in their own right and/or be hydrolysable under *in vivo* conditions in the human body. Suitable

pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. A phosphonate is formed by reaction with phosphorous (phosphonic) acid, by methods well known in the art. For example, phosphonates may be derivatives such as $RP(O)(OR)_2$ and the like. A acetate is an ester of acetic acid. A benzoate is an ester of benzenecarboxylic acid. A carbamate is an ester of carbamic acid.

In one aspect of the invention there is provided a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

10 N-[3,4-bis(methyloxy)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 N-[3,4-bis(methyloxy)phenyl]-1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-
 15 carboxamide,
 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 20 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 5-Methyl-1-(phenylmethyl)-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-(phenylmethyl)-1H-1,2,3-triazole-4-
 25 carboxamide,
 1-[(2'-Chloro-4-biphenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
 30 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-{[4-(1-methylethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide,
 N-[3,4-Bis(methyloxy)phenyl]-5-methyl-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
 1-(2-Biphenyl)methyl-N-[3,4-bis(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-
 35 carboxamide,
 N-[3,4-Bis(methyloxy)phenyl]-1-[(4-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1,3-oxazol-2-yl)phenyl]-1H-1,2,3-triazole-4-carboxamide,
 1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-
 40 carboxamide,
 Methyl 4-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-3-(methyloxy)benzoate,

- 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{3-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{4-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 5 Ethyl 3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]benzoate,
N-[3-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[4-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-
- 10 carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 15 Methyl 3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-4-(methyloxy)benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-hydroxy-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 20 Ethyl 4-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]phenyl}acetate,
Methyl 4-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-2-(methyloxy)benzoate,
Methyl 5-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-2-hydroxybenzoate,
- 25 Methyl {3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]phenyl}acetate,
1-[(3,4-Dichlorophenyl)methyl]-N-(3-hydroxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 5-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-
- 30 2-fluorobenzoate,
N-[5-(Aminocarbonyl)-2-(methyloxy)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 4-chloro-3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]benzoate,
- 35 Methyl 3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-4-(methyloxy)phenyl]acetate,
Methyl 3-[[{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl]amino]-4-fluorobenzoate,
- 40 N-[3-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[4-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,

- 1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 3-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)benzoate,
- 5 1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3-[(Acetylamino)methyl]phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-
- 10 carboxamide,
N-[4-chloro-3-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Dimethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,2-benzenedicarboxylate,
- 15 Methyl 5-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-fluorobenzoate,
Ethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-
- 20 1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 25 N-[3,5-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[5-(2-hydroxyethyl)-2-(methyloxy)phenyl]-5-methyl-1H-
- 30 1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[2-fluoro-5-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[2-chloro-5-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 35 1-[(3,5-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,5-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-
- 40 triazole-4-carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,

- N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 5 3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoic acid,
 3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methoxy)benzoic acid,
 5-[(5-Methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-benzenedicarboxylic acid,
 10 4-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoic acid,
 1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(ethylamino)carbonyl]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 15 1-[(3,4-Dichlorophenyl)methyl]-N-(3-[(2-hydroxyethyl)amino]carbonyl)phenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[5-[(methylamino)carbonyl]-2-(methoxy)phenyl]-1H-1,2,3-triazole-4-carboxamide,
 {3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}methyl acetate,
 20 {3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}methyl acetate,
 {3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}methyl benzoate,
 25 {3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}methyl benzoate,
 1-[(3,4-Dichlorophenyl)methyl]-N-{4-[(2-hydroxyethyl)oxy]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1-methylethenyl)-2-(methoxy)phenyl]-1H-1,2,3-triazole-4-carboxamide,
 30 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxy-1-methylethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 1-[(3,4-Dichlorophenyl)methyl]-N-[4-{2-(dimethylamino)ethyl}oxy]-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 35 1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(2-hydroxyethyl)oxy]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide, or
 {5-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)methyl]amino]benzene-1,3-diyl}dimethanol.
- 40 In another aspect of the invention there is provided a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:
 N-[3,4-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,

- N-[3,5-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
5 N-[3,4-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
10 1-[(3-chlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(4-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
15 1-[(3-chlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(4-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
20 1-[(3-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide
1-[(3,4-dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-5-[(methylamino)carbonyl]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, or
25 N-[1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]-4-(hydroxymethyl)benzamide.

The compounds of the invention have been found to inhibit SCD activity and may therefore be useful in regulating lipid levels, e.g. plasma lipid levels. Diseases or
30 conditions caused by or associated with an abnormal plasma lipid profile and for the treatment of which the compounds of the invention may be useful include; dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes,
35 insulin resistance, hyperinsulinaemia and metabolic syndrome. Other cardiovascular diseases for which the compounds of the present invention are useful include peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes and thrombosis. Other diseases or conditions include hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to
40 accumulation of lipids in the liver.

The compounds of the invention may also be useful in the treatment of skin disorders e.g. eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes.

- 5 The compounds of the invention may also be useful in the treatment of cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like.

- 10 The compounds of the invention may also be useful in the treatment of mild cognitive impairment (MCI), Alzheimer's disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42.

- 15 Within the context of the present invention, the terms describing the indications used herein are classified in the Merck Manual of Diagnosis and Therapy, 17th Edition and/or the International Classification of Diseases 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention.

- 20 In one aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in medical therapy.

- In one aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

- 25 In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing acne, psoriasis, skin ageing, cancer, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

- 30 In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing acne, psoriasis, skin ageing, cancer, dyslipidemia, atherosclerosis, insulin resistance, hyperinsulinaemia, Type II diabetes and/or hepatic steatosis.

- 35 In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing acne.

- 40 In one aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor in a mammal, including human.

5 In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing acne, psoriasis, skin ageing, cancer, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

10 In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing acne, psoriasis, skin ageing, cancer, dyslipidemia, atherosclerosis, insulin resistance, hyperinsulinaemia, Type II diabetes and/or hepatic steatosis.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing acne.

15 In one aspect, the invention provides a method for treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor, which method comprises administering to a subject, for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

20 In another aspect, the invention provides a method for treating and/or preventing a acne, psoriasis, skin ageing, cancer, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH), which method comprises administering to a subject, 25 for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

30 In another aspect, the invention provides a method for treating and/or preventing acne, psoriasis, skin ageing, cancer, dyslipidemia, atherosclerosis, insulin resistance, hyperinsulinaemia, Type II diabetes and/or hepatic steatosis, which method comprises administering to a subject, for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

35 In another aspect, the invention provides a method for treating and/or preventing acne, which method comprises administering to a subject, for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

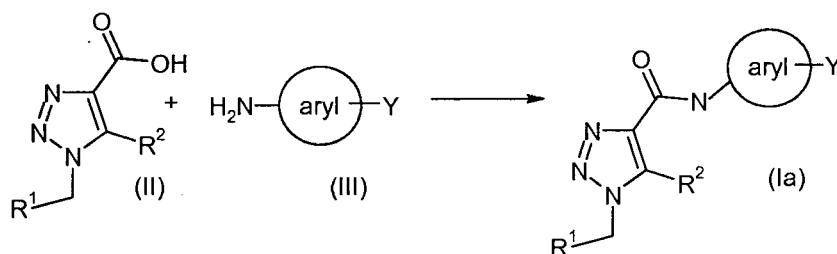
40 It will be appreciated that reference to "treatment" and "therapy" includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

- Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.
- Processes for the preparation of the compounds of formula (I) form further aspects of the invention. R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and X are as defined above unless otherwise specified. Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc.
- In certain instances final compounds of formula (I) can be converted into other compounds of formula (I) by techniques known to those in the art, for example, carboxylic acid substituents can be converted to esters or amides by routine techniques.

In a general process, compounds of formula (I), wherein X represents $-\text{CONH}-$ and R^3

- represents, $\text{aryl}-Y$, wherein aryl represents $-\text{C}_{6-10}\text{aryl}$ and Y represents $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkoxy}$, $-\text{O}(\text{CH}_2)_m\text{R}^4$, $-\text{C}_{0-6}\text{alkylOH}$, $-(\text{CH}_2)_n\text{CO}_2\text{R}^5$, $-(\text{C}=\text{O})\text{NHR}^6$, $-(\text{CH}_2)_p\text{NHC}(=\text{O})\text{R}^7$, $-\text{O}(\text{CH}_2)_q\text{NR}^8\text{R}^9$, $-\text{C}_{1-6}\text{haloalkyl}$, $-\text{OC}_{1-6}\text{haloalkyl}$, $-\text{C}_{3-6}\text{cycloalkyl}$, $-\text{OC}_{3-6}\text{cycloalkyl}$, halogen or $-\text{C}_5\text{heteroaryl}$, (formula (Ia)), may be prepared according to reaction scheme 1 by reacting compounds of formula (II) and compounds of formula (III). The reaction is suitably carried out in the presence of a coupling reagent such as HATU or EDCI and HOBt and base such as DIPEA or NEt_3 in a suitable solvent such as DMF (suitably at room temperature to 40°C).

Scheme 1



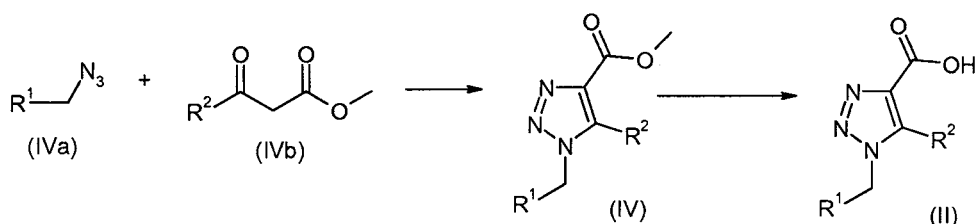
Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Ia) by reacting a compound of formula (II), wherein R^1 and R^2

are defined above, with a compound of formula (III) wherein Y and
above, in the presence of a coupling agent.

aryl

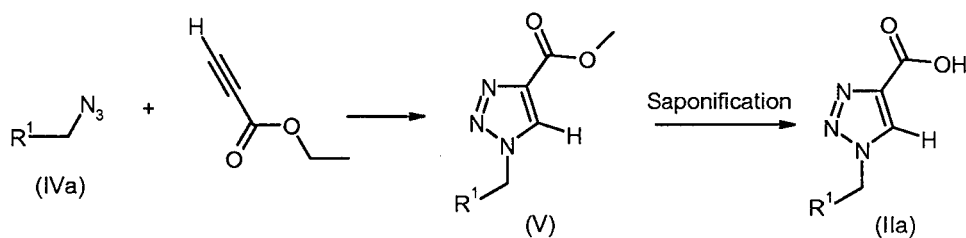
Compounds of formula (II) may be prepared according to reaction scheme 2 by reacting
5 compounds of formula (IVa) and compounds of formula (IVb). The reaction is suitably
carried out in the presence of base such as potassium carbonate in a suitable solvent
such as DMF or DMSO (suitably at 40-80°C), and is followed by saponification of
compounds of formula (IV) in basic conditions such as sodium hydroxide in a suitable
solvent, such as ethanol or methanol (to reflux).

Scheme 2



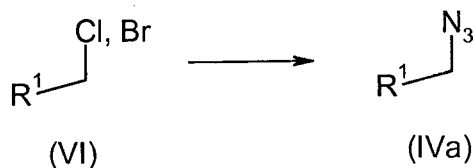
Compounds of formula (II), wherein R^2 represents H (formula (IIa)), may be prepared
according to reaction scheme 3 by reacting compounds of formula (IVa) and ethyl 2-
propynoate in a suitable solvent such as ethanol to reflux, and is followed by
saponification of compounds of formula (V) in basic conditions such as sodium hydroxide
in a suitable solvent, such as ethanol or methanol (suitably at reflux).

Scheme 3



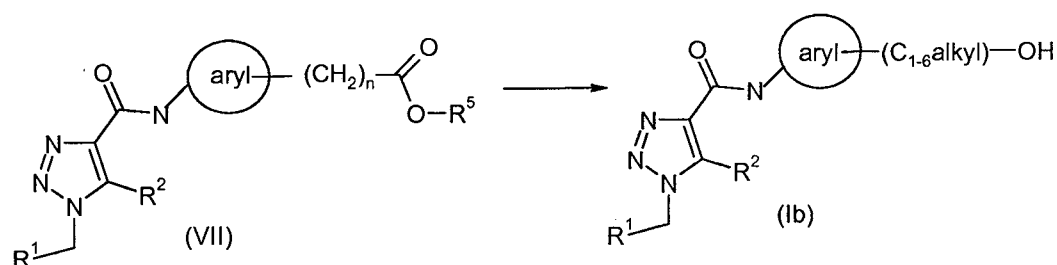
Compounds of formula (IVa) may be prepared according to reaction scheme 4 by the
reaction of benzyl halide chlorine or bromine (VI) with sodium azide in a suitable solvent
such as DMSO or DMF (suitably at room temperature to 80°C).

Scheme 4



Compounds of formula (I), wherein R^3 represents $\text{aryl}-(\text{C}_{1-6}\text{alkyl})-\text{OH}$ and aryl is defined above (formula (Ib)), may also be prepared according to reaction scheme 5 by reduction of the ester function ($\text{Y} = -(\text{CH}_2)_n\text{COOR}^5$) of compounds of formula (VII) in the presence of DIBAL-H in solution of toluene. The reaction is suitably carried out in a suitable solvent such as THF at room temperature.

Scheme 5

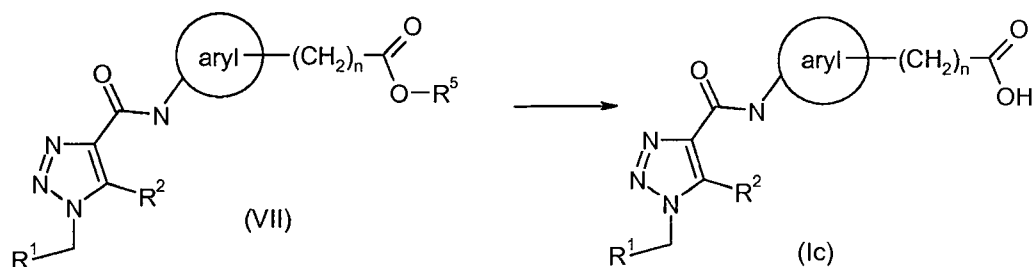


Accordingly, in another aspect the invention provides a process for the preparation of compounds of the formula (Ib) by reduction of the ester function ($\text{Y} = -(\text{CH}_2)_n\text{COOR}^5$) of

compounds of the formula (VII), wherein R^1 , R^2 and aryl are defined above.

Compounds of formula (I), wherein R^3 represents $\text{aryl}-(\text{CH}_2)_n-\text{COOH}$ and aryl is defined above (formula (Ic)), may be prepared according to reaction scheme 6 by saponification of the ester function ($\text{Y} = -(\text{CH}_2)_n\text{COOR}^5$) of compounds of the formula (VII) in basic conditions in a suitable solvent such as methanol or ethanol, suitably at reflux.

Scheme 6

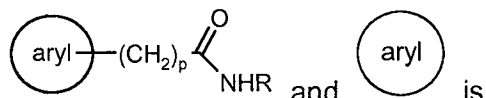


Accordingly, in another aspect the invention provides a process for the preparation of compounds of the formula (Ic) by saponification of the ester function ($Y = -(CH_2)_nCOOR^5$)

of compounds of the formula (VII), wherein R^1 , R^2 and aryl are defined above, in basic conditions.

5

Compounds of formula (I), wherein R^3 represents

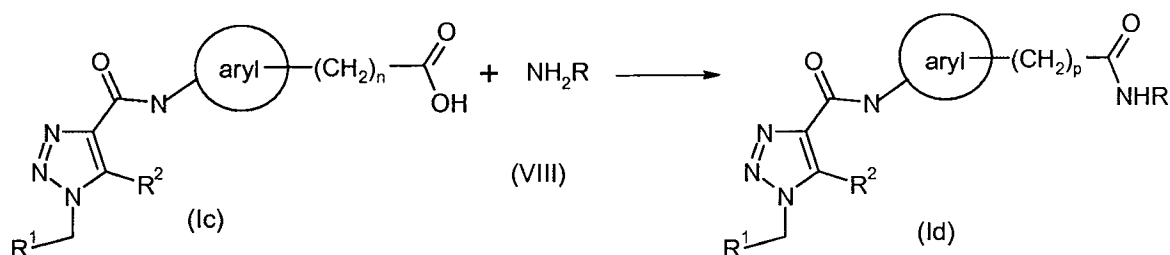


is defined above formula (Id)), may be prepared according to reaction scheme 7 by reacting compounds of formula (Ic) and compounds of formula (VIII), wherein R represents R^6 or R^7 , in the presence of a coupling reagent such as HATU, HOBT or EDCI, and a base such as DIPEA or NEt_3 in a suitable solvent such as DMF (suitably at room temperature to 40°C).

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Scheme 7

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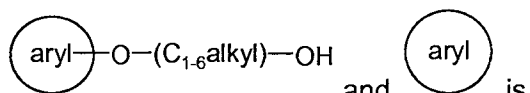
Accordingly, in another aspect the invention provides a process for the preparation of compounds of the formula (Id) by reacting compounds of formula (Ic), wherein R^1 , R^2 and



are defined above, with compounds of formula (VIII) wherein R is defined above, in the presence of a coupling agent.

20

Compounds of formula (I), wherein R^3 represents

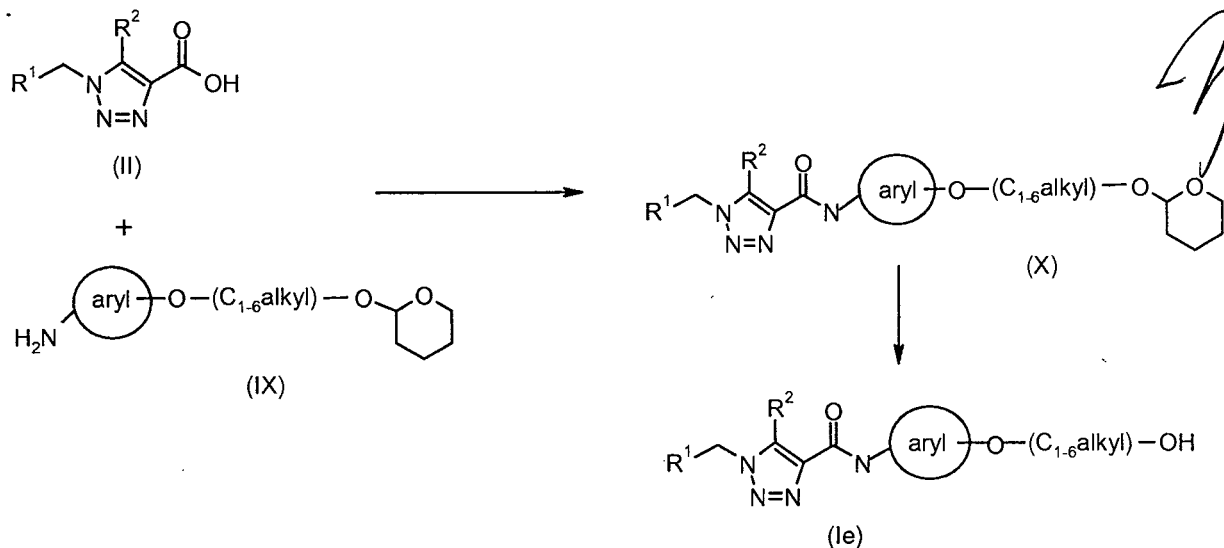


is defined above (formula (Ie)), may be prepared according to reaction scheme 8 by reacting compounds of formula (IX) and compounds of formula (II). The reaction is suitably carried out in the presence of a coupling reagent such as HATU and base such as DIPEA in a suitable solvent such as DMF (suitably at room temperature or at 40°C), and is followed by deprotection of compounds of formula (X) with a of a concentrated HCl solution in AcOEt.

25

Scheme 8

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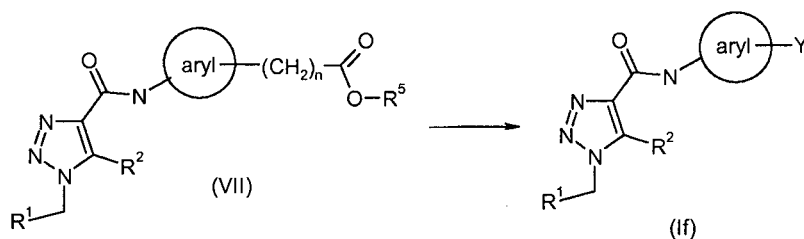


Accordingly, in another aspect the invention provides a process for the preparation of compounds of the formula (Ie) by reacting compounds of formula (II), wherein R^1 and R^2

- 5 are defined above, with compounds of formula (IX), wherein aryl is defined above, in the presence of a coupling agent, followed by the deprotection of compounds of formula (X).

- 10 Compounds of formula (I), wherein R^3 represents $\text{aryl}-Y$, aryl is defined above and Y represents branched $-C_{0-6}\text{alkylOH}$ (such as $-C(\text{CH}_3)_3\text{OH}$) (formula (If)), may be prepared according to reaction scheme 9 by reacting compounds of formula (VII) in the presence of a solution of methyl magnesium bromide in THF (suitably at room temperature or at 60°C).

15 Scheme 9

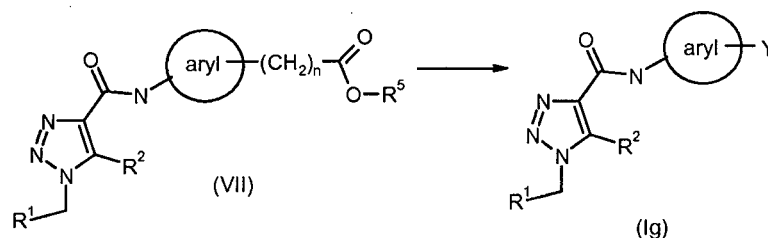


Accordingly, in another aspect the invention provides a process for the preparation of

- 20 compounds of the formula (If), wherein aryl and Y are defined above, by reacting compounds of formula (VII), wherein R^1 and R^2 are defined above, in the presence of methyl magnesium bromide.

Compounds of formula (I), wherein R^3 represents $\text{aryl}-Y$, aryl is defined above and Y represents $-C_{1-6}\text{alkenyl}$ (formula (Ig)), may be prepared according to reaction scheme 10 by reacting compounds of formula (VII) in the presence of a solution of methyl magnesium bromide in THF (suitably at room temperature or at 60°C).

Scheme 10

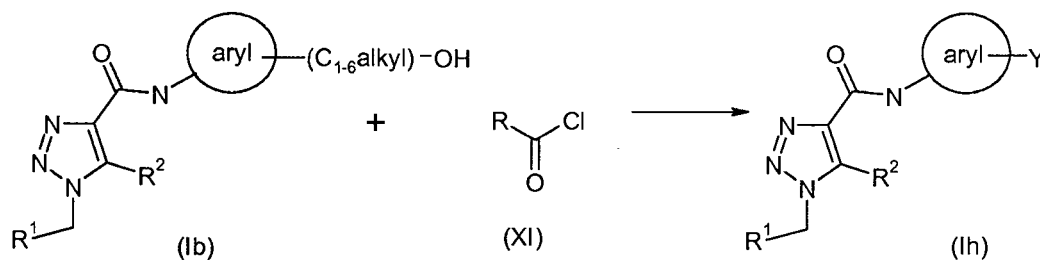


Accordingly, in another aspect the invention provides a process for the preparation of

compounds of the formula (Ig), wherein aryl and Y are defined above, by reacting compounds of formula (VII), wherein R^1 and R^2 are defined above, in the presence of methyl magnesium bromide.

Compounds of formula (I), wherein R^3 represents $\text{aryl}-Y$, aryl is defined above and Y represents $-(CH_2)_mOC(=O)R^4$ or $-(CH_2)_nOC(=O)R^5$ (formula (Ih)), may be prepared according to reaction scheme 11 by reaction of compounds of the formula (Ib) with compounds of the formula (XI), wherein R represents R^4 or R^5 , in a suitable solvent such as a mixture of DCM and THF (suitably at suitable room temperature).

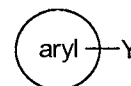
Scheme 11



Accordingly, in another aspect the invention provides a process for the preparation of

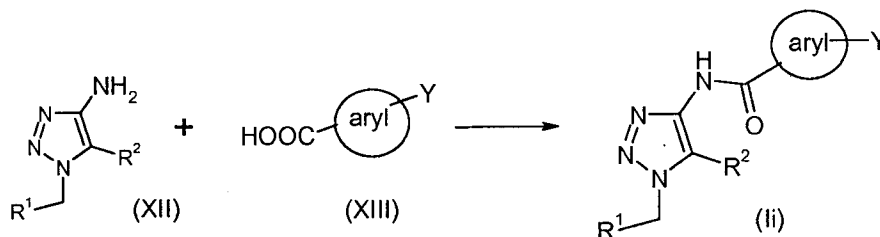
compounds of the formula (Ih), wherein aryl and Y are defined above, by reacting compounds of formula (Ib), wherein R^1 and R^2 are defined above, with compounds of the formula (XI), wherein R is defined above.

Compounds of formula (I), wherein X represents -NHCO- and R³ represents



wherein and Y are defined as above ((formula (I)), may be prepared according to reaction scheme 12 by reacting compounds of formula (XII) and compounds of formula (XIII). The reaction is suitably carried out in the presence of a coupling reagent such as HATU and a base such as DIPEA in a suitable solvent such as DCM or DMF (suitably at room temperature to 40°C).

Scheme 12



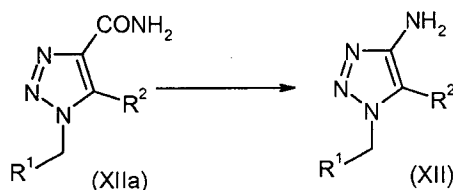
Accordingly, in another aspect the invention provides a process for the preparation of compounds of the formula (Ii) by reacting compounds of formula (XII), wherein R¹ and R²

and R³ represents , wherein and Y are defined as above, with

compounds of formula (XIII) wherein and Y are defined above, in the presence of a coupling reagent.

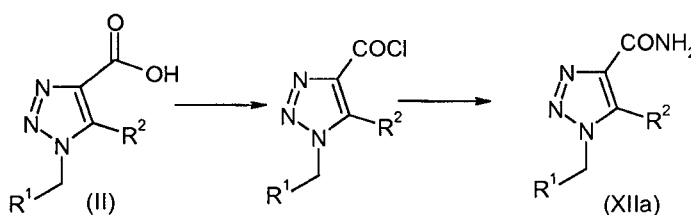
Compounds of formula (XII), wherein R¹ and R², are defined above may be prepared according to reaction scheme 13 by reacting compounds of formula (XIa) in the presence of bromine and a base such as potassium hydroxide in a suitable solvent such as water (suitably at 40° to 80°C).

Scheme 13



Compounds of formula (XIa), wherein R¹ and R², are defined above may be prepared according to reaction scheme 14 by reacting compounds of formula (Ii), in the presence of thionyl chloride in chloroform at room temperature, followed by reaction with aqueous ammonia in acetonitrile on ice (e.g. -5 to 5°C).

Scheme 14



5 Compounds of the formula (III) (IVb), (VI), (VIII), (IX), (XI) and (XIII) are commercially available compounds or may be prepared by methods known in the literature or processes known to those skilled in the art. Compounds of the formula (VII) may be prepared according to the general reaction scheme 1.

10 Further details for the preparation of compounds of formula (I) are found in the examples section hereinafter.

The compounds of the invention may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100
 15 compounds. Libraries of compounds of the invention may be prepared by a combinatorial 'split and mix' approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect there is provided a compound library comprising at least 2 compounds of the invention.

20 Those skilled in the art will appreciate that in the preparation of compounds of formula (I) and/or solvates thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule or the appropriate intermediate to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for
 25 example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g.
 30 benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropylloxycarbonyl, cyclohexyloxycarbonyl) and alkyl or aralkyl type protecting groups (e.g. benzyl, trityl, chlorotriyl).

35 Various intermediate compounds used in the above-mentioned process, including but not limited to certain compounds of formulae (IV), (V) and (X), constitute a further aspect of the present invention.

The compounds of formula (I) or pharmaceutically acceptable salt(s) thereof may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or pharmaceutically acceptable salts thereof together with one or more further therapeutic agent(s).

5

Compounds of the invention may be administered in combination with other therapeutic agents. Preferred therapeutic agents are selected from the list: an inhibitor of cholesteryl ester transferase (CETP inhibitors), a HMG-CoA reductase inhibitor, a microsomal triglyceride transfer protein, a peroxisome proliferator-activated receptor activator (PPAR), a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an inhibitor of AcylCoA: cholesterol acyltransferase (ACAT inhibitor), a cannabinoid 1 antagonist a bile acid sequestrant. Other preferred therapeutic agents are selected from the list: a corticosteroid, a vitamin D3 derivative, a retinoid, an immunomodulator, an anti androgen, a keratolytic agent, an anti-microbial, a platinum chemotherapeutic, an antimetabolite, hydroxyurea, a taxane, a mitotic disrupter, an anthracycline, dactinomycin, an alkylating agent and a cholinesterase inhibitor.

20

When the compound of formula (I) or pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

25

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with at least one pharmaceutically acceptable carrier and/or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

30

When administration is sequential, either the SCD inhibitor or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

35

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

40

The invention also includes a pharmaceutical composition comprising one or more compounds of formula (I) or pharmaceutically acceptable salt (s) in combination with one or more excipients.

5 The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

10

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

15 The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

20

25 Creams, lotions, or ointments, may be prepared as rinse-off or leave-on products, as well as two stage treatment products for use with other skin cleansing or managing compositions. The compositions can be administered as a rinse-off product in a higher concentration form, such as a gel, and then a leave-on product in a lower concentration to avoid irritation of the skin. Each of these forms is well understood by those of ordinary skill in the art, such that dosages may be easily prepared to incorporate the pharmaceutical composition of the invention.

30

Ointments are hydrocarbon-based semisolid formulations containing dissolved or suspended drugs. Creams and lotions are semi-solid emulsion systems and the term is applied both to water/oil or oil/water. Gel formulations are semi-solid systems in which a liquid phase is trapped in a polymeric matrix.

35

By way of non-limiting example, the ointments may contain one or more hydrophobic carriers selected from, for example, white soft paraffin or other mineral waxes, liquid paraffin, non-mineral waxes, long chain alcohols, long chain acids and silicones. The ointment may contain in addition to the hydrophobic carriers some hydrophilic carriers selected from, for example, propylene glycol and polyethylene glycol in combination with an appropriate surfactant/co-surfactant system. The carrier compositions of the creams or lotions are typically based on water, white soft paraffin and an appropriate surfactant/co-surfactant system, in combination with other carriers/components selected from, for

40

example, propylene glycol, butylene glycol glycerinemonostearate, PEG-glycerinemonostearate, esters such as C₁₂₋₁₅ alkyl benzoate, liquid paraffin, non-mineral waxes, long chain alcohols, long chain acids silicones, non-silicone polymers. The gels may by way of example be formulated using isopropyl alcohol or ethyl alcohol, propylene glycol and water with a gelling agent such as hydroxyethyl cellulose, suitably in combination with minor components, for example one or more of butylene glycol and a wetting agent such as a poloxamer.

An ointment, cream, lotion, gel, and the like, can further comprise a moisturizing agent. The moisturizing agent can be a hydrophobic moisturizing agent such as ceramide, borage oil, tocopherol, tocopherol linoleate, dimethicone or a mixture thereof or a hydrophilic moisturizing agent such as glycerine, hyaluronic acid, sodium peroxylinecarbolic acid, wheat protein, hair keratin amino acids, or a mixture thereof.

The compositions according to the invention may also comprise conventional additives and adjuvants for dermatological applications, such as preservatives, acids or bases used as pH buffer excipients and antioxidants.

The present invention encompasses administration via a transdermal patch or other forms of transdermal administration. Suitable formulations for transdermal administration are known in the art, and may be employed in the methods of the present invention. For example, suitable transdermal patch formulations for the administration of a pharmaceutical compound are described in, for example, U.S. Pat. No. 4, 460,372 to Campbell et al., U.S. Pat. No. 4,573,996 to Kwiatak et al., U. S. Pat. No. 4,624,665 to Nuwayser, U.S. Pat. No. 4,722,941 to Eckert et al., and U.S. Pat. No. 5, 223,261 to Nelson et al.

One suitable type of transdermal patch for use in the methods of the present invention encompasses a suitable transdermal patch includes a backing layer which is non-permeable, a permeable surface layer, an adhesive layer substantially continuously coating the permeable surface layer, and a reservoir located or sandwiched between the backing layer and the permeable surface layer such that the backing layer extends around the sides of the reservoir and is joined to the permeable surface layer at the edges of the permeable surface layer. The reservoir contains a compound of formula (I) or pharmaceutically acceptable salt thereof, alone or in combination, and is in fluid contact with the permeable surface layer. The transdermal patch is adhered to the skin by the adhesive layer on the permeable surface layer, such that the permeable surface layer is in substantially continuous contact with the skin when the transdermal patch is adhered to the skin. While the transdermal patch is adhered to the skin of the subject, the compound of formula (I) or pharmaceutically acceptable salt thereof contained in the reservoir of the transdermal patch is transferred via the permeable surface layer, from the reservoir, through the adhesive layer, and to the skin of the patient. The transdermal patch may optionally also include one or more penetration-enhancing agents in the reservoir that

enhance the penetration of the compound of formula (I) or pharmaceutically acceptable salt thereof through the skin.

5 Examples of suitable materials which may comprise the backing layer are well known in the art of transdermal patch delivery, and any conventional backing layer material may be employed in the transdermal patch of the instant invention.

10 Suitable penetration-enhancing agents are well known in the art as well. Examples of conventional penetration-enhancing agents include alkanols such as ethanol, hexanol, cyclohexanol, and the like, hydrocarbons such as hexane, cyclohexane, isopropylbenzene; aldehydes and ketones such as cyclohexanone, acetamide, N,N-di(lower alkyl)acetamides such as N,N-diethylacetamide, N,N-dimethyl acetamide, N-(2-hydroxyethyl) acetamide, esters such as N,N-di-lower alkyl sulfoxides; essential oils such as propylene glycol, glycerine, glycerol monolaurate, isopropyl myristate, and ethyl oleate, 15 salicylates, and mixtures of any of the above.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, 20 maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, 25 emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example 30 almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

35 Preparations for oral administration may be suitably formulated to give controlled/extended release of the active compound.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

40 For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing

solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active ingredient, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognised by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The invention also extends to novel intermediates disclosed herein, used in the preparation of compounds of formula (I) or salts thereof.

The following is a list of the used definitions:

DEFINITIONS

APTS	para toluene sulfonic acid
AcOEt	ethyl acetate
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride solution
DIPEA	diisopropylethylamine

ys

- | | | |
|----|--------------------|--|
| | DME | 1,2-dimethoxy ethane |
| | DMF | dimethylformamide |
| | DMSO | dimethyl sulfoxide |
| | EDCI | 1,3-Propanediamine, N3-(ethylcarbonimidoyl)-N1,N1-dimethyl-, |
| 5 | | hydrochloride |
| | NEt ₃ | triethylamine |
| | EtOH | ethanol |
| | HATU | O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium |
| | | hexafluorophosphate |
| 10 | HCl | hydrochloric acid |
| | HOBt | 1-hydroxy benzotriazole |
| | NaOH | sodium hydroxide |
| | NH ₄ Cl | ammonium chloride |
| | PBr ₃ | phosphorus tribromine |
| 15 | Pd tetrakis | tetrakis(triphenylphosphine)palladium (0) |
| | Pd/C | palladium (0) on carbon |
| | RT | room temperature |
| | THF | tetrahydrofuran |
- 20 Regardless of how the preparation of compounds are represented in the present specification no inference can be drawn that particular batches (or mixtures of two or more batches) of intermediates were used in the next stage of the preparation. The examples and intermediates are intended to illustrate the synthetic routes suitable for preparation of the same, to assist the skilled persons understanding of the present invention.

25

Where reference is made to the use of a "similar" procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variation, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

30

Analytical methods LC-MS

35 Analytical HPLC was conducted on a X-terra MS C18 column (2,5 µm 3 * 30 mm id) eluting with 0,01M ammonium acetate in water (solvent A) and 100% acetonitrile using the following elution gradient: 0 to 4 minutes, 5 to 100%B; 4 to 5 minutes, 100%B at a flowrate of 1,1 mL/min with a temperature of 40°C.

40 The mass spectra (MS) were recorded on a micromass ZQ-LC mass spectrometer using electrospray positive ionisation [ES+ve to give MH⁺ molecular ion] or electrospray negative ionisation [ES-ve to give (M-H)⁻ molecular ion] modes.

Analytical methods LC-HRMS

Analytical HPLC was conducted on an Uptisphere-hsc column (3 μ m 30 * 3 mm id) eluting with 0,01M ammonium acetate in water (solvent A) and 100% acetonitrile (solvent B) using the following elution gradient: 0 to 0,5 minutes, 5%B; 0,5 to 3,5 minutes, 5 to 100%B; 3,5 to 4 minutes, 100%B; 4 to 4,5 minutes, 100 to 5%B; 4,5 to 5,5 minutes, 5%B at a flowrate of 1,3 mL/min with a temperature of 40°C.

The mass spectra (MS) were recorded on a micromass LCT, mass spectrometer using electrospray positive ionisation [ES+ve to give MH^+ molecular ion] or electrospray negative ionisation [ES-ve to give $(M-H)^-$ molecular ion] modes.

Analytical method GC-MS

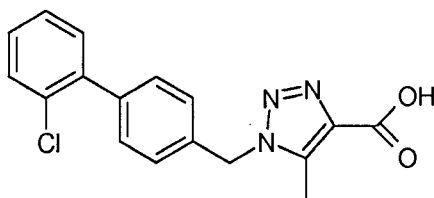
Analytical GC was conducted on a DB-1ms column (Agilent Technologies), 0.1 μ m 10m * 0.1mm id) eluting with an Helium flow of 0.5ml/min and pressure at 3.4 bar and with a gradient temperature: 0 to 0.35 min, 100°C; 0.35min to 6min, 100°C to 250°C (ramp of 80°C/min).

The mass spectra (MS) were recorded on a Agilent Technologies G5973 mass spectrometer using electronic impact ionisation.

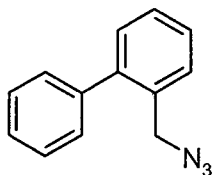
Supporting Examples and Intermediates

The invention is illustrated by the non-limiting Examples described below.

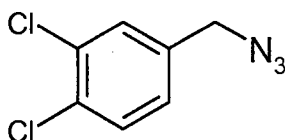
Intermediate 1: 1-[(2'-Chloro-4-biphenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid



To a solution of 1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (0.2 g, 0.67 mmol) in DME (10 mL) were added (2-chlorophenyl)boronic acid, (0.137g, 0.88 mmol), Pd tetrakis (20 mg, 10% mol/mol) and a 2M solution of sodium carbonate (1.34 mL, 4 eq). The reaction was heated at 85°C for 48 hours. After evaporation of DME, water was added and the reaction was extracted with ethyl acetate (2 x 40 mL). The aqueous phase was adjusted to PH = 7 by addition of a 1N HCl solution and extracted with ethyl acetate. The combined organic phases were dried over sodium sulphate and evaporated in vacuo to give the title compound as a solid (117 mg, 40%). HRMS calculated for $C_{17}H_{14}ClN_3O_2 (M+H)^+$ 328.0853, found: 328.0865, Rt: 2.04 min.

Intermediate 2: 2-Biphenylmethyl azide

- 5 To a solution of 2-(bromomethyl)biphenyl (1.5 g, 6 mmol) in DMSO (15 mL) was added sodium azide (0.59 g, 9 mmol) and a catalytic amount of sodium iodide. The mixture was stirred at room temperature for 2 days. After concentration under reduced pressure, the residue was diluted with ethyl acetate. The organic layer was washed with brine (2 x 60 mL), dried on sodium sulphate and after filtration was evaporated to dryness to give the title compound as an oil (1.1 g, 87%). ¹H NMR (300 MHz, CDCl₃, ppm) δ: 7.56-7.38 (m, 9H), 4.37 (s, 2H).

Intermediate 3: (3,4-Dichlorophenyl)methyl azide

15

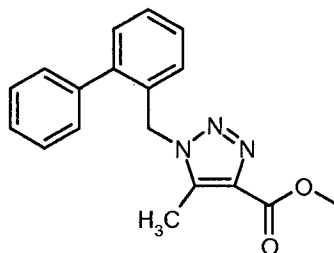
- A mixture of 3,4-dichlorobenzyl chloride (10 g, 0.05 mol), sodium azide (5 g, 0.08 mol) in DMSO (100 mL) was stirred at room temperature overnight. The mixture was poured into water (150 mL). The water layer was extracted with ethyl acetate (100 ml x 3). The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by distillation to give the title compound as an oil (14 g, quantitative yield). LC/MS: m/z 203 (M+H)⁺, Rt: 2.26 min.

- The following compounds were similarly prepared by a method analogous to that described for Intermediate 3:

Table 1

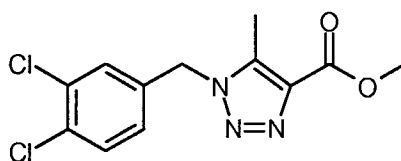
Compound	Structure	From	Physical data
Intermediate 4 (3,5-Dichlorophenyl) methyl azide		3,4-dichlorobenzyl chloride	Not isolated
Intermediate 5 (3-Chlorophenyl) methyl azide		3-chlorobenzyl bromide	LC/MS: m/z 168 (M+H) ⁺ , Rt: 2.54 min

Intermediate 6: Methyl 1-(2-biphenylmethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate



- 5 To a solution of 2-biphenylmethyl azide (Intermediate 2) (1.1 g, 5.2 mmol) and methyl acetoacetate (0.9 g, 7.8 mmol) in DMSO (10 mL) was added potassium carbonate (2.9 g, 20 mmol). The reaction mixture was stirred at 40°C for 48 hours. After cooling, water was added and the mixture was extracted with ethyl acetate, the organic layer was dried on sodium sulphate and after filtration was evaporated to dryness. The residue was purified by flash column chromatography eluting with DCM and DCM/MeOH: 98/2 to give the title compound as an oil (1.1 g, 68.7%). LC/MS: m/z 308 (M+H)⁺, Rt: 3.14 min.

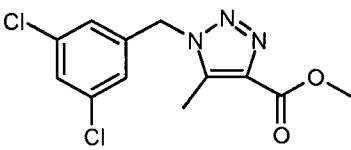
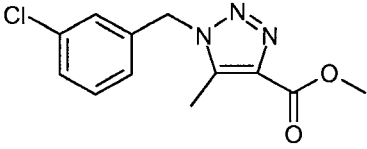
Intermediate 7: Methyl 1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylate



- 15 To a suspension of milled potassium carbonate (38.7 g, 0.28 mol) in DMSO (100 mL) was added (3,4-dichlorophenyl)methyl azide (Intermediate 3) (14 g, 0.07 mol) and methyl acetoacetate (12.1 g, 0.1 mol). The mixture was stirred at 40°C for 48 hours. The mixture was poured into a mixture of ice and water (100 mL). The water was extracted with ethyl acetate (100 mL x 2). The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by distillation to give the title compound as white solid crystals (14 g, 67%). LC/MS: m/z 301 (M+H)⁺, Rt: 1.97 min.

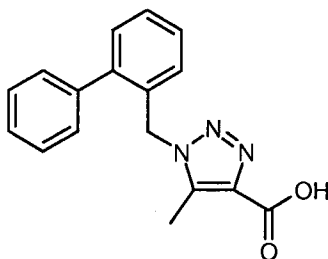
25 The following compounds were similarly prepared by a method analogous to that described for Intermediate 7:

Table 2

Compound	Structure	From	Physical data
Intermediate 8 Methyl 1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylate		(3,5-dichlorophenyl)methyl azide (Intermediate 4)	LC/MS: m/z 300 (M+H) ⁺ , Rt: 3.01 min
Intermediate 9 Methyl 1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylate		(3-chlorophenyl)methyl azide (Intermediate 5)	¹ H NMR (300 MHz, DMSO, ppm) δ: 7.39 (dd, 2H), 7.3 (s, 1H) 5.65 (s, 2H), 3.81 (s, 3H), 2.46 (s, 3H).

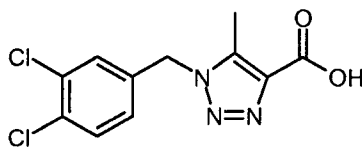
Intermediate 10: 1-(2-Biphenylmethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid

5



To a solution of methyl 1-(2-biphenylmethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (Intermediate 6) (1.1 g, 3.58 mmol) in methanol was added an aqueous solution of sodium hydroxide (7.2 mL, 6 mmol). The solution was heated at reflux for 3 hours. After concentration under reduced pressure, a 1N HCl solution (8 mL) was added. The resulting solid material was filtered, washed with water and dried to give the title compound as a cream solid (810 mg, 77%). LC/MS: m/z 294 (M+H)⁺, Rt: 2.23 min.

Intermediate 11: 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid



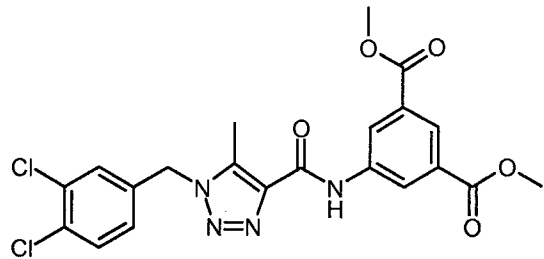
To a mixture of methyl 1-[(3,4-dichlorophenyl)methyl]-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (Intermediate 7) (9 g, 0.03 mol) in methanol (200 mL) was added NaOH (2.4 g) and water. The mixture was stirred overnight. Water was added and the solvent was evaporated. The residue was extracted with DCM (twice). The aqueous phase was adjusted to pH=2 with a 2N HCl solution. The formed precipitate was filtered to give the title compound as a white solid (7.29 g, 84%). LC/MS: m/z 287 (M+H)⁺, Rt: 2.52 min.

The following compounds were similarly prepared by a method analogous to that described for Intermediate 11:

Table 3

Compound	Structure	From	Physical data
Intermediate 12 1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1 <i>H</i> -1,2,3-triazole-4-carboxylic acid		Methyl 1-[(3,5-dichlorophenyl)methyl]-5-methyl-1 <i>H</i> -1,2,3-triazole-4-carboxylate (Intermediate 8)	LC/MS: m/z 286 (M+H) ⁺ , Rt: 2.22 min
Intermediate 13 1-[(3-Chlorophenyl)methyl]-5-methyl-1 <i>H</i> -1,2,3-triazole-4-carboxylic acid		Methyl 1-[(3-chlorophenyl)methyl]-5-methyl-1 <i>H</i> -1,2,3-triazole-4-carboxylate (Intermediate 9)	¹ H NMR (300 MHz, DMSO, ppm) δ: 7.37-7.27 (dd, 2H), 7.11 (s, 1H) 5.63 (s, 2H), 2.44 (s, 3H).

Intermediate 14: Dimethyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1*H*-1,2,3-triazol-4-yl)carbonyl)amino]-1,3-benzenedicarboxylate



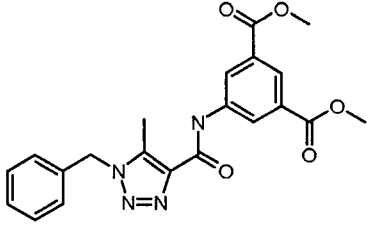
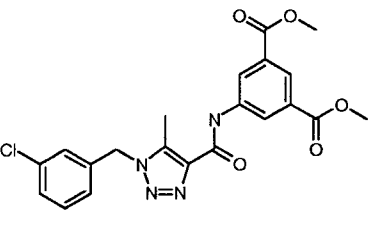
A mixture of 1-[(3,4-dichlorophenyl)methyl]-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (Intermediate 11) (0.4 g, 1.3 mmol), dimethyl 5-amino-1,3-benzenedicarboxylate (0.29 g, 1 eq), HATU (0.69 g, 1.3 eq) and DIPEA (0.34 mL, 1.3 eq) in DMF (10 mL) was stirred at 45°C for 24 hours. The solvent was evaporated and the residue was washed with water

and extracted with DCM. The organic phase was dried over sodium sulphate and concentrated. The title compound was obtained as a white solid (650 mg, 95%) after recrystallisation from acetonitrile. LC/MS: m/z 477 (M+H)⁺, Rt: 3.81 min.

51

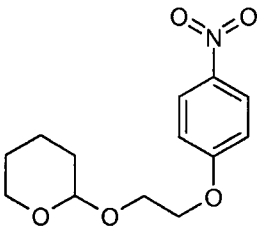
- 5 The following compounds were similarly prepared by a method analogous to that described for Intermediate 14:

Table 4

Compound	Structure	From	Physical data
Intermediate 15 Dimethyl 5-({[5-methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl]carbonyl}amino)-1,3-benzenedicarboxylate		5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxylic acid and dimethyl 5-amino-1,3-benzene dicarboxylate	LC/MS: m/z 409 (M+H) ⁺ , Rt: 3.34 min
Intermediate 16 Dimethyl 5-({[1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl}amino)-1,3-benzenedicarboxylate		1-[(3-Chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 13) and dimethyl 5-amino-1,3-benzene dicarboxylate	LC/MS: m/z 443 (M+H) ⁺ , Rt: 3.54 min

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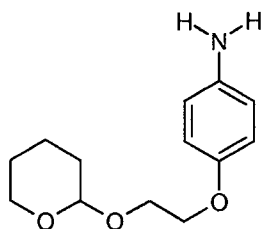
Intermediate 17: 2-({2-[(4-Nitrophenyl)oxy]ethyl}oxy)tetrahydro-2H-pyran



- 15 To a solution of 2-[(4-Nitrophenyl)oxy]ethanol (1 g, 5.4 mmol), in toluene (50 mL) was added 3,4-dihydro-2H-pyran (1.5 mL) and APTS (catalytic amount). The reaction was stirred at 60°C for 3 hours. The dark solution was then concentrated and purified by flash chromatography using DCM/cyclohexane 30/70 as eluent. The title compound was obtained as an oil (1.33 g, 92%). LC: Rt: 3.12 min.

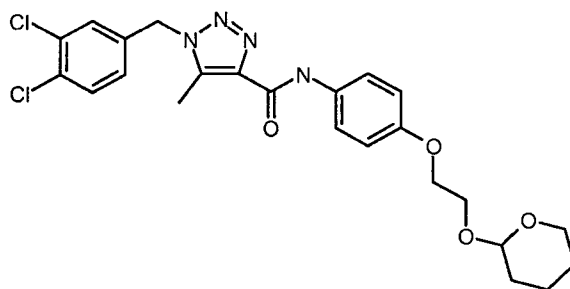
20

Intermediate 18: 4-{[2-(Tetrahydro-2H-pyran-2-yloxy)ethyl]oxy}aniline



To a solution of 2-([2-(4-nitrophenyl)oxy]ethyl)oxy)tetrahydro-2H-pyran (Intermediate 17) (1.33 g, 5 mmol) in EtOH (50 mL) was added Pd/C (catalytic amount) and ammonium formate (0.9 g, 10 eq). The reaction was stirred to 40°C for 2 hours. After filtration on celite, the solvent was evaporated and the residue was poured in water, extracted with ether and dried over sodium sulphate and evaporated. The title compound was obtained as a dark oil (0.8 g, 68%). LC/MS: m/z 238 (M+H)⁺, Rt: 2.38 min.

Intermediate 19: 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-(4-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]oxy}phenyl)-1H-1,2,3-triazole-4-carboxamide



A mixture of 1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) (0.3 g, 1 mmol), 4-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]oxy}aniline (Intermediate 18) (0.28 g, 1.2 eq), HATU (0.8 g, 2 eq), and NEt₃ (440 µL, 3 eq) in DMF was stirred at 45°C for 18 hours. The solvent was evaporated and the residue was washed with water and extracted with a mixture of ether and ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated in vacuo. The title compound was obtained and used in the next step without purification and isolation.

The following compounds were similarly prepared by a method analogous to that described for Intermediate 14:

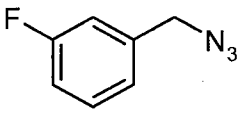
Table 5

Compound	Structure	From	Physical data
Intermediate 20 Dimethyl 4-({[5-methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl]carbonyl}amino)-1,2-benzenedicarboxylate		5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxylic acid and dimethyl 4-amino-1,2-benzenedicarboxylate	LC/MS: m/z 407 (M-H) ⁺ , Rt: 2.74 min
Intermediate 21 Dimethyl 5-({[1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl}amino)-1,3-benzenedicarboxylate		1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and dimethyl 5-amino-1,3-benzenedicarboxylate	LC/MS: m/z 427 (M+H) ⁺ , Rt: 3.44 min
Intermediate 22 Dimethyl 4-({[1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl}amino)-1,2-benzenedicarboxylate		1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 13) and dimethyl 4-amino-1,2-benzenedicarboxylate	LC/MS: m/z 443 (M+H) ⁺ , Rt: 3.36 min
Intermediate 23 Dimethyl 4-({[1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl}amino)-1,2-benzenedicarboxylate		1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and dimethyl 4-amino-1,2-benzenedicarboxylate	LC/MS: m/z 427 (M+H) ⁺ , Rt: 3.22 min

5 The following compound was similarly prepared by a method analogous to that described for Intermediate 3:

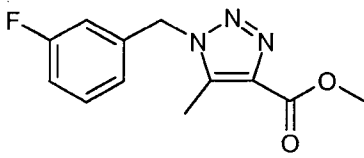
91

Table 6

Compound	Structure	From	Physical data
Intermediate 24 (3-fluorophenyl) methyl azide		3-fluorobenzyl bromide	Not isolated

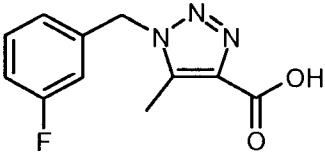
5 The following compound was similarly prepared by a method analogous to that described for Intermediate 7:

Table 7

Compound	Structure	From	Physical data
Intermediate 25 Methyl 1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylate		(3-fluorophenyl) methyl azide (Intermediate 24)	LC/MS: m/z 250 (M+H) ⁺ , Rt: 2.61 min

10 The following compound was similarly prepared by a method analogous to that described for Intermediate 11:

Table 8

Compound	Structure	From	Physical data
Intermediate 26 1-[(3-Fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid		methyl 1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylate (Intermediate 25)	LC/MS: m/z 236 (M+H) ⁺ , Rt: 1.56 min

15 The following compounds were similarly prepared by a method analogous to that described for Intermediate 14

Table 9

Compound	Structure	From	Physical data
Intermediate 27 Dimethyl 5-[(1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,3-benzenedicarboxylate		1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 26) and dimethyl 5-amino-1,3-benzenedicarboxylate	LC/MS: m/z 427 (M+H) ⁺ , Rt: 3.35 min
Intermediate 28 Dimethyl 4-[(1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,2-benzenedicarboxylate		1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 26) and dimethyl 5-amino-1,2-benzenedicarboxylate	LC/MS: m/z 427 (M+H) ⁺ , Rt: 3.21 min

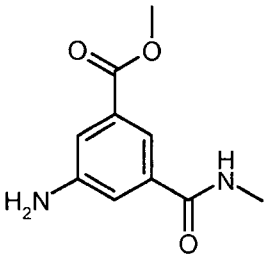
The following compound was similarly prepared by a method analogous to that described for Intermediate 19:

5

Table 10

Compound	Structure	From	Physical data
Intermediate 29 Methyl 3-[(methylamino)carbonyl]-5-nitrobenzoate		3-[(methoxy)carbonyl]-5-nitrobenzoic acid and methylamine	LC/MS: m/z 239 (M+H) ⁺ , Rt: 2.26 min

Intermediate 30: Methyl 3-amino-5-[(methylamino)carbonyl]benzoate



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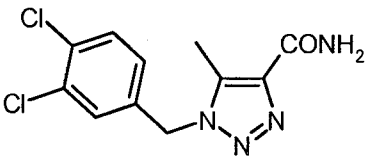
To a solution of methyl 3-[(methylamino)carbonyl]-5-nitrobenzoate (Intermediate 29) (1.33 g, 5.59 mmol), in ethanol (30 mL) were added ammonium formate (3.52 g, 1eq.) and Pd/C (catalytic quantity). The reaction was stirred at 40°C for one night. After filtration on celite, the solvent was evaporated in vacuo. The residue was dissolved in DCM, washed with water, dried over sodium sulfate and concentrated to give the title compound as a white solid (0.56 g, 48.3%). LC/MS: m/z 209 (M+H)⁺, Rt: 1.50 min.

The following compound was similarly prepared by a method analogous to that described for Intermediate 14

Table 11

Compound	Structure	From	Physical data
Intermediate 31 Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-5-[(methylamino)carbonyl]benzoate		1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 3-amino-5-[(methylamino)carbonyl]benzoate (Intermediate 30)	LC/MS: m/z 476 (M+H) ⁺ , Rt: 3.15 min

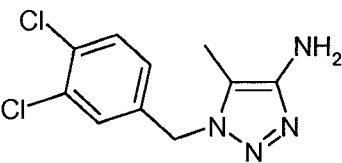
Intermediate 32: 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide



To a solution of (1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid) (Intermediate 11) (14 g, 48.93 mmol), in chloroform (200 mL) was added thionyl chloride (30 mL) at room temperature. The reaction mixture was stirred to reflux for 4 hours and concentrated in vacuum. The mixture was then dissolved in acetonitrile (50 mL) and aqueous ammonia (50 mL) was added at 0°C for 30 min. The resulting solid was filtered and dried to give the title compound as white crystals. (12.7 g, 91.1%). LC/MS: m/z 285 (M+H)⁺, Rt: 2.53 min.

Intermediate 33: 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-amine

57



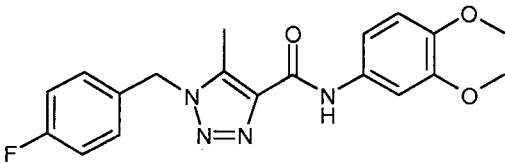
To a solution of potassium hydroxide (10.96 g, 195.8 mmol) in water (50 mL), cooled in an ice-salt bath, was added bromine (6.3 g, 32.16 mmol) and at 0°C, 1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide (Intermediate 32) (9.3 g, 32.63 mmol) was added for 4 hours under vigorous stirring. The reaction mixture was then warmed at 80°C for 2 days and stirred at room temperature for 12 hours. The resulting solid was filtered and purified by HPLC to give the title compound (3.45 g, 41.14%). LC/MS: m/z 257 (M+H)⁺. Rt: 2.25 min.

The following compounds were similarly prepared by a method analogous to that described for Intermediate 14

Table 12

Compound	Structure	From	Physical data
Intermediate 34 Methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)amino)carbonyl] benzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-amine (Intermediate 33) and 4-[(methyloxy)carbonyl] benzoic acid	LC/MS: m/z 419 (M+H) ⁺ , Rt: 3.11 min

Example 1: N-[3,4-bis(Methyloxy)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide



A mixture of 1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (0.2 g, 0.85 mmol), 3,4-bis(methyloxy)aniline (0.156 g, 1.2 eq), HATU (0.485 g, 1.5 eq) and DIPEA (240 µL, 1.5 eq) in DMF was stirred at room temperature overnight. The solvent was evaporated and the residue was washed with water and extracted with DCM. The organic phase was dried over sodium sulphate, filtered and concentrated in vacuo. The

residue was purified by flash column chromatography eluting with DCM to give after precipitation from ether, the title compound as a white solid (180 mg, 57%). HRMS calculated for $C_{19}H_{19}FN_4O_3$ ($M+H$)⁺ 371.1519, found: 371.1500, Rt: 2.78 min. MP: 119.7°C.

5

The following compounds were similarly prepared by analogous method to that described for Example 1:

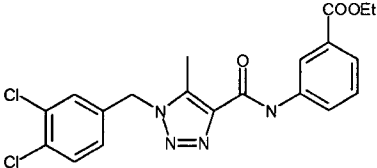
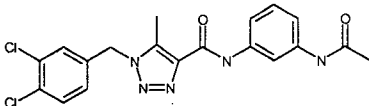
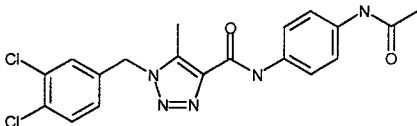
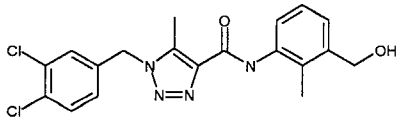
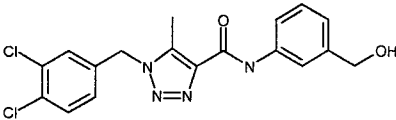
Table 13

Compound	Structure	From	Physical data
Example 2 N-[3,4-bis(methoxy)phenyl]-1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and 3,4-bis(methoxy)aniline	HRMS calculated for $C_{19}H_{19}BrN_4O_3$ Theo : 431.0719 Found: 431.0684 Rt: 2.93 min. MP: 173°C
Example 3 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide		1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and 4-[(phenylmethyl)oxy]aniline	HRMS calculated for $C_{24}H_{21}BrN_4O_2$ Theo : 477.0926 Found: 477.0963 Rt: 3.49 min. MP: 168.7°C
Example 4 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide		1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and 4-[(phenylmethyl)oxy]aniline	HRMS calculated for $C_{24}H_{21}FN_4O_2$ Theo : 417.1727 Found: 417.1768 Rt: 3.32 min. MP: 139.4°C
Example 5 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide		1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and 4-[(3-methylbutyl)oxy]aniline	HRMS calculated for $C_{22}H_{25}FN_4O_2$ Theo : 397.2040 Found: 397.2061

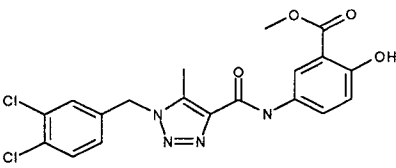
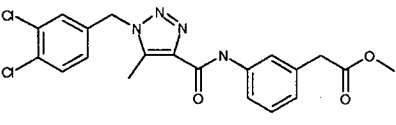
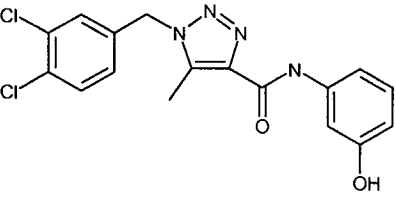
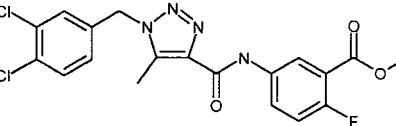
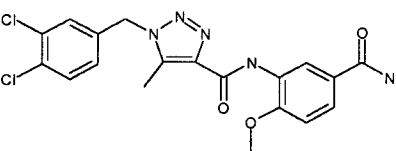
Compound	Structure	From	Physical data
phenyl}-1H-1,2,3-triazole-4-carboxamide		methylbutyl)oxy] aniline	Rt: 3.58 min MP: 114°C
Example 6 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide		1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and 4-[(3-methylbutyl)oxy]aniline	HRMS calculated for $C_{22}H_{25}BrN_4O_2$ Theo : 457.1239 Found: 457.1256 Rt: 3.76 min MP: 137°C
Example 7 5-Methyl-1-(phenylmethyl)-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxylic acid and 4-[(phenylmethyl)oxy]aniline	HRMS calculated for $C_{24}H_{22}N_4O_2$ Theo : 399.1821 Found: 399.1819 Rt: 3.34 min MP: 125°C
Example 8 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxylic acid and 4-[(3-methylbutyl)oxy]aniline	HRMS calculated for $C_{22}H_{26}N_4O_2$ Theo : 379.2134 Found: 379.2165 Rt: 3.55 min MP: 124°C
Example 9 1-[(2'-Chloro-4-biphenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide		1-[(2'-chloro-4-biphenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 1) and 4-[(3-methylbutyl)oxy]aniline	HRMS calculated for $C_{28}H_{29}ClN_4O_2$ Theo : 489.2057 Found: 489.2104 Rt: 3.99 min MP: 125°C (decomposition)
Example 10 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxylic acid and 4-[(3-methylbutyl)oxy]aniline	HRMS calculated for $C_{23}H_{28}N_4O_2$ Theo : 393.2290 Found:

Compound	Structure	From	Physical data
methylphenyl)methyl]-1H-1,2,3-triazole- 4-carboxamide		methylbutyl)oxy] aniline	393.2285 Rt: 3.70 min MP: 105°C
Example 11 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[(4-(1-methylethyl)phenyl)methyl]-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-[(4-(1-methylethyl)phenyl)methyl]-1H-1,2,3-triazole-4-carboxylic acid and 4-[(3-methylbutyl)oxy]aniline	HRMS calculated for $C_{25}H_{32}N_4O_2$ Theo : 421.2603 Found: 421.2585 Rt: 3.93 min MP: 114°C (decomposition)
Example 12 N-[3,4-bis(Methyloxy)phenyl]-5-methyl-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxylic acid and 3,4-bis(methyloxy)aniline	HRMS calculated for $C_{20}H_{22}N_4O_3$ Theo : 367.1770 Found: 367.1751 Rt: 2.88 min MP: 156°C (decomposition)
Example 13 1-(2-biphenylmethyl)-N-[3,4-bis(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-(2-biphenylmethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 10) and 3,4-bis(methyloxy)aniline	HRMS calculated for $C_{25}H_{24}N_4O_3$ Theo 429.1927 Found: 429.1937 Rt: 3.2 min MP: 121°C
Example 14 N-[3,4-bis(Methyloxy)phenyl]-1-[(4-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxamide		1-[(4-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxylic acid 3,4-bis(methyloxy)aniline	HRMS calculated for $C_{18}H_{17}N_4O_3$ Theo 357.1363 Found: 357.1355 Rt: 2.55 min MP: 197.8°C
Example 15 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid	HRMS calculated for $C_{20}H_{15}Cl_2N_5O_2$ Theo : 428.0681 Found:

Compound	Structure	From	Physical data
[4-(1,3-oxazol-2-yl)phenyl]-1H-1,2,3-triazole-4-carboxamide		(Intermediate 11) and 4-(1,3-oxazol-2-yl)aniline	428.0716 Rt: 3.14 min. MP: 218°C
Example 16 1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and (4-aminophenyl)methanol	HRMS calculated for C ₁₈ H ₁₆ Cl ₂ N ₄ O ₂ Theo : 391.0728 Found: 391.0755 Rt: 2.77 min MP: 183°C
Example 17 Methyl 4-[[[1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]-3-(methoxy)benzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 4-amino-3-(methoxy)benzoate	HRMS calculated for C ₂₀ H ₁₈ Cl ₂ N ₄ O ₄ Theo : 449.0783 Found: 449.0813 Rt: 3.42 min MP: 212°C
Example 18 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{3-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide		methyl 1-(2-biphenylmethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (Intermediate 6) and 3-amino-N-methylbenzamide	HRMS calculated for C ₁₉ H ₁₇ Cl ₂ N ₅ O ₂ Theo : 418.0837 Found: 418.0851 Rt: 2.74 min MP: 203.9°C
Example 19 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{4-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and 4-amino-N-methylbenzamide	HRMS calculated for C ₁₉ H ₁₇ Cl ₂ N ₅ O ₂ Theo : 418.0837 Found: 418.0839 Rt: 2.71 min MP: 183.7°C

Compound	Structure	From	Physical data
Example 20 Ethyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and ethyl 3-aminobenzoate	HRMS calculated for $C_{20}H_{18}Cl_2N_4O_3$ Theo : 433.0834 Found: 433.0797 Rt: 3.38 min MP: 131.8°C
Example 21 N-[3-(Acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and N-(3-aminophenyl)acetamide	HRMS calculated for $C_{19}H_{17}Cl_2N_5O_2$ Theo : 418.0837 Found: 418.0830 Rt: 2.78 min MP: 203.4°C
Example 22 N-[4-(Acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and N-(4-aminophenyl)acetamide	HRMS calculated for $C_{19}H_{17}Cl_2N_5O_2$ Theo : 418.0837 Found: 418.0840 Rt: 2.72 min MP: 202.4°C
Example 23 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and (3-amino-2-methylphenyl)methanol	HRMS calculated for $C_{19}H_{18}Cl_2N_4O_2$ Theo : 405.0885 Found: 405.0878 Rt: 2.78 min MP: 174.3°C
Example 24 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11)	HRMS calculated for $C_{18}H_{16}Cl_2N_4O_2$ Theo : 391.0728 Found: 391.0695

Compound	Structure	From	Physical data
nyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		and (3-aminophenyl) methanol	Rt: 2.78 min MP: 185.2°C
Example 25 Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methoxy)benzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 3-amino-4-(methoxy)benzoate	HRMS calculated for $C_{20}H_{18}Cl_2N_4O_4$ Theo : 449.0783 Found: 449.0802 Rt: 3.36 min MP: 203°C
Example 26 1-[(3,4-Dichlorophenyl)methyl]-N-[4-hydroxy-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and 4-amino-2-(hydroxymethyl)phenol	HRMS calculated for $C_{18}H_{16}Cl_2N_4O_3$ Theo : 407.0677 Found: 407.0683 Rt: 2.57 min MP: 175.6°C
Example 27 Ethyl {4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}acetate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and ethyl (4-aminophenyl)acetate	HRMS calculated for $C_{21}H_{20}Cl_2N_4O_3$ Theo : 447.0990 Found: 447.0975 Rt: 3.25 min MP: 139°C
Example 28 Methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-(methoxy)benzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 4-amino-2-(methoxy)benzoate	HRMS calculated for $C_{20}H_{18}Cl_2N_4O_4$ Theo : 449.0783 Found: 449.0787 Rt: 3.1 min MP: 175.9°C

Compound	Structure	From	Physical data
Example 29 Methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]-2-hydroxybenzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 5-amino-2-hydroxybenzoate	HRMS calculated for $C_{19}H_{16}Cl_2N_4O_4$ Theo : 435.0627 Found: 435.0638 Rt: 3.2 min MP: 180°C
Example 30 Methyl {3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]phenyl}acetate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl (3-aminophenyl)acetate	HRMS calculated for $C_{20}H_{18}Cl_2N_4O_3$ Theo : 433.0834 Found: 433.0825 Rt: 3.14 min MP: 116°C
Example 31 1-[(3,4-Dichlorophenyl)methyl]-N-(3-hydroxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and 3-aminophenol	HRMS calculated for $C_{17}H_{14}Cl_2N_4O_2$ Theo : 377.0572 Found: 377.0593 Rt: 2.86 min MP: 192.5°C
Example 32 Methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]-2-fluorobenzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 5-amino-2-fluorobenzoate	HRMS calculated for $C_{19}H_{15}Cl_2FN_4O_3$ Theo : 437.0583 Found: 437.0544 Rt: 3.22 min MP: 169.8°C
Example 33 N-[5-(Aminocarbonyl)-2-(methoxy)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and 3-amino-4-(methoxy)	HRMS calculated for $C_{19}H_{17}Cl_2N_5O_3$ Theo : 434.0786 Found: 434.0773 Rt: 2.77 min MP: 218.2°C

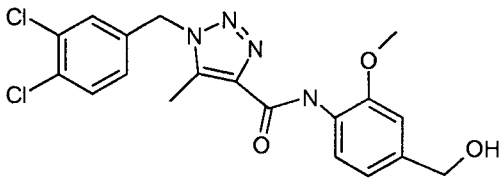
Compound	Structure	From	Physical data
1H-1,2,3-triazole-4-carboxamide		benzamide	
Example 34 Methyl 4-chloro-3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 3-amino-4-chlorobenzoate	HRMS calculated for $C_{19}H_{15}Cl_3N_4O_3$ Theo : 453.0288 Found: 453.0330 Rt: 3.59 min MP: 206.4°C
Example 35 Methyl [3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methoxy)phenyl]acetate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl [3-amino-4-(methoxy)phenyl]acetate	HRMS calculated for $C_{21}H_{20}Cl_2N_4O_4$ Theo : 463.0940 Found: 463.0985 Rt: 3.29 min MP: 133°C
Example 36 Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-fluorobenzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and methyl 3-amino-4-fluorobenzoate	HRMS calculated for $C_{19}H_{15}Cl_2FN_4O_3$ Theo : 437.0583 Found: 437.0624 Rt: 3.37 min MP: 195.7°C
Example 37 N-[3-(Hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxylic acid (commercially available) and (3-aminophenyl)methanol	HRMS calculated for $C_{18}H_{18}N_4O_2$ Theo : 323.1508 Found: 323.1529 Rt: 2.45 min MP: 105.8°C
Example 38 N-[4-(Hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxylic acid (commercially available) and (4-aminophenyl)methanol	HRMS calculated for $C_{18}H_{18}N_4O_2$ Theo : 323.1508 Found:

Compound	Structure	From	Physical data
(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide		available) and (4-aminophenyl) methanol	323.1504 Rt: 2.42 min MP: 149.1°C
Example 39 N-[3-(Hydroxymethyl)-2-methylphenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide		5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxylic acid (commercially available) and (3-amino-2-methylphenyl) methanol	HRMS calculated for $C_{19}H_{20}N_4O_2$ Theo : 337.1664 Found: 337.1654 Rt: 2.44 min MP: 157°C
Example 40 1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 12) and (3-aminophenyl) methanol	HRMS calculated for $C_{18}H_{16}Cl_2N_4O_2$ Theo : 391.0728 Found: 391.0726 Rt: 2.84 min MP: 159°C
Example 41 Methyl 3-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonylamino]-4-(methoxy)benzoate		1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 12) and methyl 3-amino-4-(methoxy)benzoate	HRMS calculated for $C_{20}H_{18}Cl_2N_4O_4$ Theo : 449.0783 Found: 449.0783 Rt: 3.44 min MP: 213°C
Example 42 1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 12) and (3-amino-2-methylphenyl) methanol	HRMS calculated for $C_{19}H_{18}Cl_2N_4O_2$ Theo : 405.0885 Found: 405.0860 Rt: 2.83 min MP: 185°C

Compound	Structure	From	Physical data
Example 43 N-{3-[(Acetylamino) methyl]phenyl}-1-[(3,4-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and N-[(3-aminophenyl) methyl]acetamide	HRMS calculated for $C_{20}H_{19}Cl_2N_5O_2$ Theo : 432.0994 Found: 432.1003 Rt: 2.83 min MP: 188.4°C
Example 44 1-[(3,4-Dichlorophenyl) methyl]-N-[3-(1-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and 1-(3-aminophenyl) ethanol	HRMS calculated for $C_{19}H_{18}Cl_2N_4O_2$ Theo : 405.0885 Found: 405.0869 Rt: 2.97 min MP: 145°C
Example 45 N-[4-Chloro-3-(hydroxymethyl) phenyl]-1-[(3,4-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3,4-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and (5-amino-2-chlorophenyl) methanol	HRMS calculated for $C_{18}H_{15}Cl_3N_4O_2$ Theo : 425.0339 Found: 425.0315 Rt: 3.12 min MP: 190.3°C
Example 46 Dimethyl 4-[(1-[(3,4-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino-1,2-benzene dicarboxylate		1-[(3,4-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and dimethyl 4-amino-1,2-benzene dicarboxylate	HRMS calculated for $C_{21}H_{18}Cl_2N_4O_5$ Theo : 477.0732 Found: 477.0703 Rt: 3.23 min MP: 148°C
Example 47 Methyl 5-[(1-[(3,5-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazol-4-		1-[(3,5-dichlorophenyl) methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 12)	HRMS calculated for $C_{19}H_{15}Cl_2FN_4O_3$ Theo : 437.0583 Found: 437.0562

Compound	Structure	From	Physical data
yl}carbonyl)amino]-2-fluorobenzoate		and methyl 5-amino-2-fluorobenzoate	Rt: 3.29min MP: 191°C
Example 48 Ethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]benzoate		1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 11) and ethyl 4-aminobenzoate	HRMS calculated for C ₂₀ H ₁₈ Cl ₂ N ₄ O ₃ Theo : 433.0834 Found: 433.0830 Rt: 3.37 min MP: 167°C

Example 49: 1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)-2-(methoxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide



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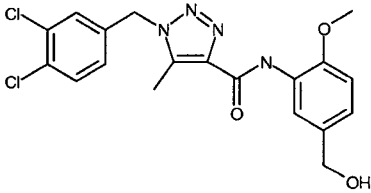
To a solution of methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]-3-(methoxy)benzoate (Example 17) (0.1 g, 0.2 mmol) in THF was added a 1M solution of DIBAL-H in THF (800 µL, 4 eq) and the reaction was stirred to room temperature for 2 hours. Solid NH₄Cl was added followed by water and a 1N HCl solution. The aqueous phase was extracted with ether and AcOEt, dried over sodium sulphate and evaporated. After recrystallisation from acetonitrile, the title compound was obtained as a white solid (30 mg, 35%). HRMS calculated for C₁₉H₁₈Cl₂N₄O₃ (M+H)⁺ 421.0834, found: 421.0834, Rt: 2.94 min. MP: 136°C.

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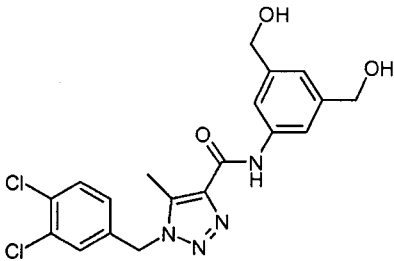
The following compounds were similarly prepared by analogous method to that described for Example 49:

Table 14

Compound	Structure	From	Physical data
Example 50 1-[(3,4-Dichlorophenyl)methyl]-N-[4-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-		Ethyl {4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}carbonyl)amino]phenyl}acetate (Example 27)	HRMS calculated for C ₁₉ H ₁₈ Cl ₂ N ₄ O ₂ Theo : 405.0885 Found: 405.0885 Rt: 2.79 min. MP: 144°C

Compound	Structure	From	Physical data
carboxamide			
Example 51 1-[(3,4-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)benzoate (Example 25)	HRMS calculated for C ₁₉ H ₁₈ Cl ₂ N ₄ O ₃ Theo : 421.0834 Found: 421.0794 Rt: 2.91 min. MP: 198°C

Example 52: N-[3,5-bis(Hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide



5

To a solution of dimethyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,3-benzenedicarboxylate (Intermediate 14) (0.65 g, 1.3 mmol) in THF (40 mL), was added a 1M solution of DIBAL-H in toluene (10 mL, 7 eq) and the reaction was stirred to room temperature for 2 hours. Solid NH₄Cl was added and the reaction mixture was stirred at RT for 30 min. The aqueous phase was extracted with ether and AcOEt, dried over sodium sulphate and evaporated. After recrystallisation from acetonitrile, the title compound was obtained as a white solid (240 mg, 44%). HRMS calculated for C₁₉H₁₈Cl₂N₄O₃ (M+H)⁺ 421.0834, found: 421.0833, Rt: 2.51 min. MP: 194.5°C.

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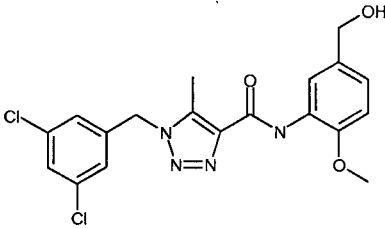
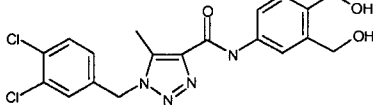
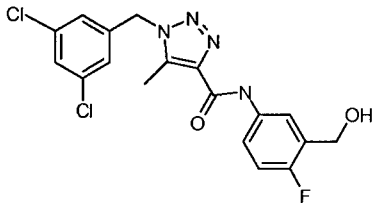
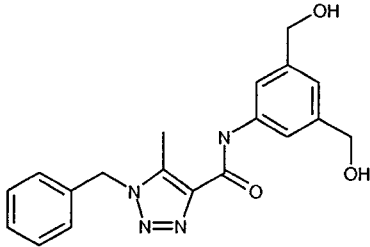
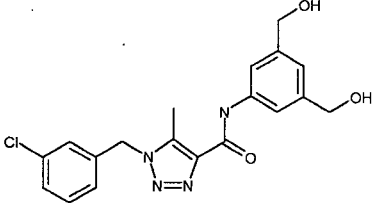
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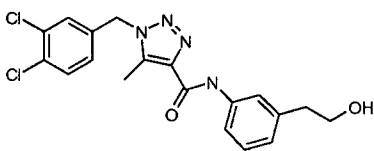
The following compounds were similarly prepared by analogous method to that described for Example 49:

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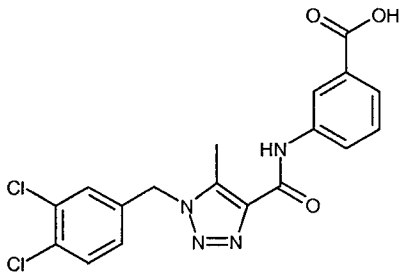
Table 15

Compound	Structure	From	Physical data
Example 53 1-[(3,4-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-fluorobenzoate (Example 32)	HRMS calculated for C ₁₈ H ₁₅ Cl ₂ FN ₄ O ₂ Theo : 409.0634 Found: 409.0617 Rt: 2.87 min. MP: 189.7°C
Example 54 1-[(3,4-Dichlorophenyl)methyl]-N-[5-(2-hydroxyethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		methyl [3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)phenyl]acetate (Example 35)	HRMS calculated for C ₂₀ H ₂₀ Cl ₂ N ₄ O ₃ Theo : 435.0991 Found: 435.0975 Rt: 3.01 min. MP: 138°C
Example 55 1-[(3,4-Dichlorophenyl)methyl]-N-[2-fluoro-5-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-fluorobenzoate (Example 36)	HRMS calculated for C ₁₈ H ₁₅ Cl ₂ FN ₄ O ₂ Theo : 409.0634 Found: 409.0624 Rt: 2.92 min. MP: 210.5°C
Example 56 N-[2-Chloro-5-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		methyl 4-chloro-3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate (Example 34)	HRMS calculated for C ₁₈ H ₁₅ Cl ₃ N ₄ O ₂ Theo : 425.0339 Found: 425.0339 Rt: 3.11 min. MP: 220°C

Compound	Structure	From	Physical data
Example 57 1-[(3,5-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methoxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		methyl 3-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methoxy)benzoate (Example 41)	HRMS calculated for $C_{19}H_{18}Cl_2N_4O_3$ Theo : 421.0834 Found: 421.0807 Rt: 2.99 min. MP: 214°C
Example 58 N-[3,4-bis(Hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		dimethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,2-benzene dicarboxylate (Example 46)	HRMS calculated for $C_{19}H_{18}Cl_2N_4O_3$ Theo : 421.0834 Found: 421.0875 Rt: 2.60 min. MP: 203°C
Example 59 1-[(3,5-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		methyl 5-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-fluorobenzoate (Example 47)	HRMS calculated for $C_{18}H_{15}Cl_2FN_4O_2$ Theo : 409.0634 found: 409.0630 Rt: 2.92 min. MP: 178°C
Example 60 N-[3,5-bis(Hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide		dimethyl 5-[(5-methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-benzene dicarboxylate (Intermediate 15)	HRMS calculated for $C_{19}H_{20}N_4O_3$ Theo : 353.1613 Found: 353.1628 Rt: 2.21 min. MP: 148.2°C
Example 61 -[3,5-bis(Hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-		dimethyl 5-[(1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-benzene	HRMS calculated for $C_{19}H_{19}ClN_4O_3$ Theo : 387.1224 Found: 387.1198

Compound	Structure	From	Physical data
5-methyl-1H-1,2,3-triazole-4-carboxamide		dicarboxylate (Intermediate 16)	Rt: 2.37 min. MP: 192.7°C
Example 62 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		methyl {3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]phenyl}acetate (Example 30)	HRMS calculated for C ₁₉ H ₁₈ Cl ₂ N ₄ O ₂ Theo : 405.0885 Found: 405.0869 Rt: 2.84 min. MP: 142°C

Example 63: 3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]benzoic acid



5

A mixture of ethyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino] benzoate (Example 20) (0.06 g, 0.138 mmol) and a 1N NaOH solution (2 mL, 2 mmol) in ethanol (5 mL) was stirred at 40°C for 4 hours. The solvent was evaporated and the residue was acidified with a 1N HCl solution. The precipitate formed was filtered and dried. The title compound was obtained as a white solid (53 mg, 96%). HRMS calculated for C₁₈H₁₄Cl₂N₄O₅ (M+H)⁺: 405.0521, found: 405.0520, Rt: 2.23 min. MP: 267.6°C.

The following compounds were similarly prepared by analogous method to that described for Example 63:

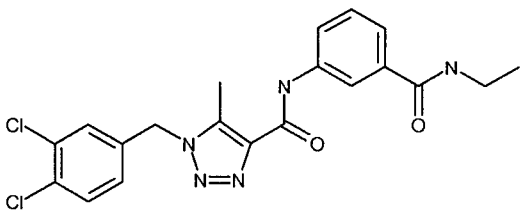
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Table 16

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Compound	Structure	From	Physical data
Example 64 3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methoxy) benzoic acid		methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methoxy) benzoate (Example 25)	HRMS calculated for C ₁₉ H ₁₆ Cl ₂ N ₄ O ₄ Theo: 435.0627 Found: 435.0630 Rt: 2.41 min MP: 243.9°C
Example 65 5-([5-Methyl-1-(phenylmethyl)-1,2,3-triazol-4-yl]carbonyl)amino)-1,3-benzene dicarboxylic acid		dimethyl 5-([5-methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl]carbonyl)amino)-1,3-benzene dicarboxylate (Intermediate 15)	HRMS calculated for C ₁₉ H ₁₆ N ₄ O ₅ Theo: 381.1199 Found: 381.1231 Rt: 1.59 min MP: 307.2°C
Example 66 4-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino] benzoic acid		ethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino] benzoate (Example 48)	HRMS calculated for C ₁₈ H ₁₄ Cl ₂ N ₄ O ₃ Theo: 405.0521 Found: 405.0531 Rt: 2.33 min MP>260°C

5 Example 67: 1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(ethylamino)carbonyl]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide



10 A mixture of 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoic acid (Example 63) (0.143 g, 0.35 mmol), ethylamine in THF, 2M solution (1.75 mL, 0.35 mmol), HATU (0.199 g, 0.52 mmol) and DIPEA (0.09 mL, 0.52 mmol) in DMF was stirred at 40°C for 1 week. The solvent was evaporated and the residue was washed with water and extracted with DCM. The organic phase was dried

over sodium sulphate, filtered and concentrated. The title compound was obtained after recrystallisation from acetonitrile as white solid (49 mg, 32%). HRMS calculated for C₂₀H₁₉Cl₂N₅O₂ (M+H)⁺ 432.0994, found: 432.0957, Rt: 2.82 min. MP: 192.2°C.

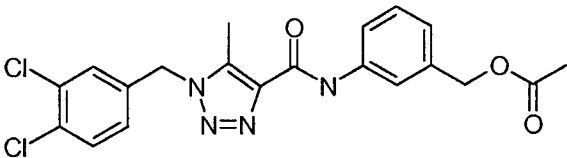
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- 5 The following compounds were similarly prepared by analogous method to that described for Example 67:

Table 17

Compound	Structure	From	Physical data
Example 68 1-[(3,4-Dichlorophenyl)methyl]-N-(3-[(2-hydroxyethyl)amino]carbonyl)phenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide		3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]benzoic acid (Example 63) and 2-aminoethanol	HRMS calculated for C ₂₀ H ₁₉ Cl ₂ N ₅ O ₃ Theo: 448.0943 Found: 448.0940 Rt: 2.57 min. MP: 190.7°C
Example 69 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[5-[(methylamino)carbonyl]-2-(methyloxy)phenyl]-1H-1,2,3-triazole-4-carboxamide		3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]-4-(methyloxy)benzoic acid (Example 64) and methyl amine	HRMS calculated for C ₂₀ H ₁₉ Cl ₂ N ₅ O ₃ Theo: 448.0943 Found: 448.0935 Rt: 2.87 min. MP: 222.2°C

- 10 Example 70: {3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]phenyl}methyl acetate

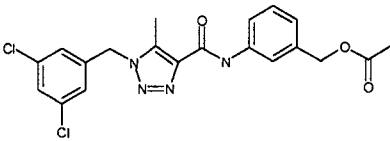
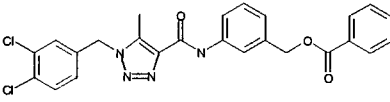
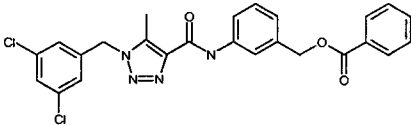


- 15 To a solution of 1-[(3,4-dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide (Example 24) (0.1 g, 0.25 mmol) in a mixture of DCM/THF were added NEt₃ (75 µL, 2 eq) and acetyl chloride (25 µL, 1.2 eq). The reaction was stirred at room temperature for 2 hours. Water was added and the product was extracted with ether, dried over sodium sulphate and evaporated in vacuo. The title compound was

obtained as a white solid after recrystallisation from isopropyl ether (a couple drops of DCM) (60 mg, 54.5%). HRMS calculated for C₂₀H₁₈Cl₂N₄O₃ (M+H)⁺ 433.0834, found: 433.0812, Rt: 3.14 min. MP: >70°C (sticky).

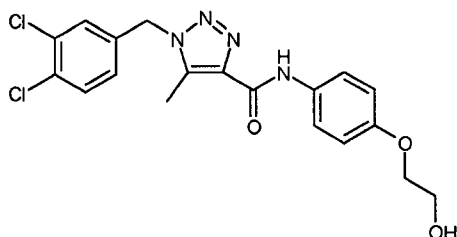
- 5 The following compounds were similarly prepared by a method analogous to that described for Example 70:

Table 18

Compound	Structure	From	Physical data
Example 71 {3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]phenyl)methyl acetate		1-[(3,5-dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide (Example 40)	HRMS calculated for C ₂₀ H ₁₈ Cl ₂ N ₄ O ₃ Theo: 433.0834 Found: 433.0801 Rt: 3.24 min. MP: 124°C
Example 72 {3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]phenyl)methyl benzoate		1-[(3,4-dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide (Example 24) and benzoyl chloride	HRMS calculated for C ₂₅ H ₂₀ Cl ₂ N ₄ O ₃ Theo: 495.0991 Found: 495.0982 Rt: 3.58 min. MP: 140°C
Example 73 {3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl)amino]phenyl)methyl benzoate		1-[(3,5-dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide (Example 40) and benzoyl chloride	HRMS calculated for C ₂₅ H ₂₀ Cl ₂ N ₄ O ₃ Theo: 495.0991 Found: 495.1003 Rt: 3.71 min. MP: 85-95°C

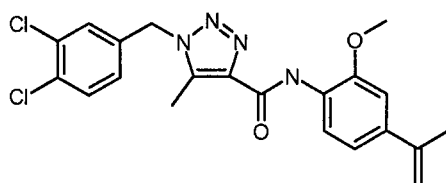
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Example 74: 1-[(3,4-Dichlorophenyl)methyl]-N-{4-[(2-hydroxyethyl)oxy]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide



To a solution of the crude 1-[(3,4-dichlorophenyl)methyl]-5-methyl-N-(4-[(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)oxy]phenyl)-1H-1,2,3-triazole-4-carboxamide (Intermediate 19) in methanol was added a saturated solution of HCl in ethyl acetate. The reaction was stirred to 60°C for 18 hours. After evaporation, the title compound was obtained as a cream solid after recrystallisation from methanol (0.23 g, 54% from intermediate 6). HRMS calculated for $C_{19}H_{18}Cl_2N_4O_3$ ($M+H$)⁺ 421.0834, found: 421.0837, Rt: 2.76 min. MP: 140°C.

Example 75: 1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1-methylethenyl)-2-(methyloxy)phenyl]-1H-1,2,3-triazole-4-carboxamide



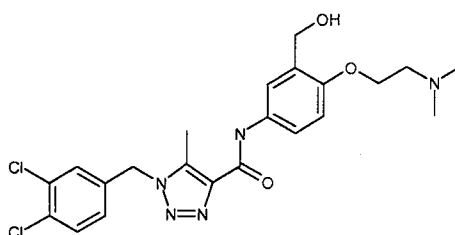
To a solution of methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-3-(methyloxy)benzoate (Example 17) (0.2 g, 0.45 mmol) in THF (30 mL) was added a 1M solution of methyl magnesium bromide in THF (5 eq). The reaction was stirred at room temperature for 2 hours and heated to 60°C for 2 hours. After cooling, water was added followed by a 1N HCl solution and the compound was extracted with ether, dried over sodium sulphate and evaporated. After purification by flash chromatography eluting with DCM and DCM/MeOH 92/8, the title compound was obtained as a white solid (0.02 g, 10%). HRMS calculated for $C_{21}H_{20}Cl_2N_4O_2$ ($M+H$)⁺ 431.1042, found: 431.1028, Rt: 3.69 min. MP: 170°C.

The following compounds were similarly prepared by analogous method to that described for Example 75:

Table 19

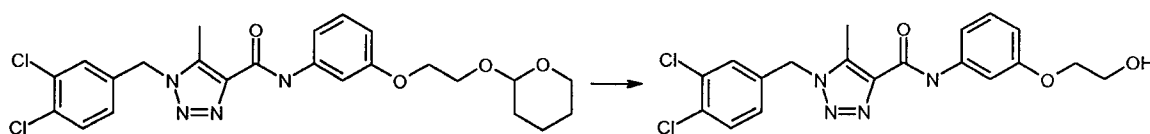
Compound	Structure	From	Physical data
Example 76 1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxy-1-methylethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		ethyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate (Example 20)	HRMS calculated for $C_{20}H_{20}Cl_2N_4O_2$ Theo: 417.0885 Found: 417.0886 Rt: 2.95 min. MP: 58°C

5 Example 77: 1-[(3,4-Dichlorophenyl)methyl]-N-[4-[[2-(dimethylamino)ethyl]oxy]-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide



10 To a solution of 1-[(3,4-dichlorophenyl)methyl]-N-[4-hydroxy-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide (Example 26) (0.1 g, 0.245 mmol) in DMF (10 mL), were added potassium carbonate (0.07 g, 2 eq) and (2-chloroethyl)dimethylamine hydrochloride (0.07 g, 2 eq). The reaction was heated at 40°C for 3 days. After evaporation, the residue was diluted with DCM, washed with water and dried over sodium sulphate. After purification by flash chromatography eluting with DCM/MeOH (90/10) and recrystallisation from methanol, the title compound was obtained as a white solid (18 mg, 16%). HRMS calculated for $C_{22}H_{25}Cl_2N_5O_3$ (M+H)⁺ 478.1413, found: 478.1435, Rt: 2.47 min. MP: 163.1°C.

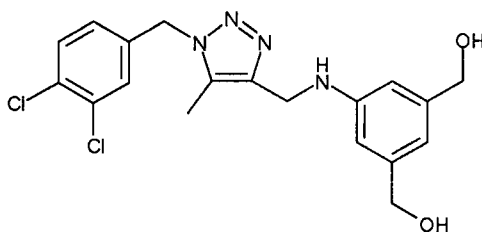
20 Example 78: 1-[(3,4-Dichlorophenyl)methyl]-N-[3-[(2-hydroxyethyl)oxy]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide



25 To a solution of 1-[(3,4-dichlorophenyl)methyl]-N-(3-hydroxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide (Example 31) (0.1 g, 0.29 mmol) in acetonitrile (10 mL) and a

couple of drops of DMF, were added 2-[(2-bromoethyl)oxy]tetrahydro-2H-pyran (0.09 μ l, 2 eq) and potassium carbonate (0.08 g, 2 eq). The reaction was heated at 40°C for 1 week. After evaporation, the residue was dissolved in DCM, washed with water and dried over sodium sulphate. After purification by flash chromatography eluting with DCM/MeOH, 98/2, the crude compound was dissolved in MeOH and some drops of a concentrated HCl solution in AcOEt were added and the solution was stirred at room temperature for 3 hours. After evaporation, the compound was recrystallised (twice) from methanol and washed with a mixture of ether and pentane. The title compound was obtained as a green solid (45 mg, 36%). HRMS calculated for $C_{19}H_{18}Cl_2N_4O_3$ (M+H)⁺ 421.0834, found: 421.0804, Rt: 2.87 min. MP: 144.9°C.

Example 79: {5-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)methyl]amino]benzene-1,3-diyl}dimethanol



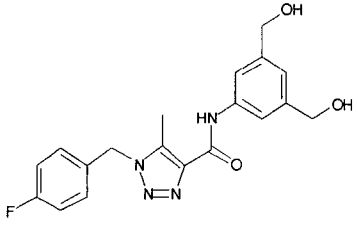
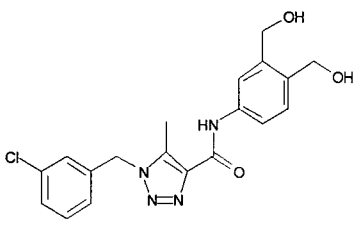
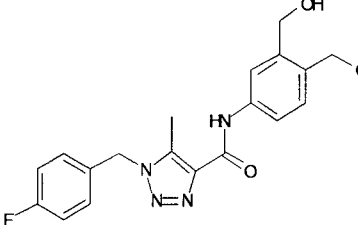
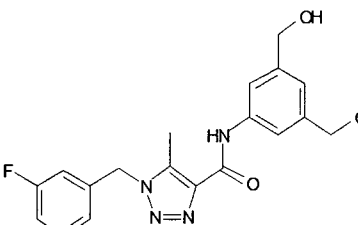
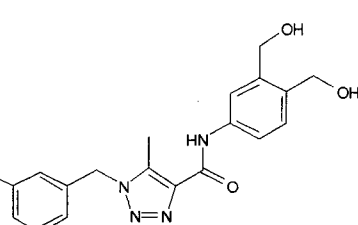
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This compound was obtained as a by product of the reduction of dimethyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,3-benzenedicarboxylate (Intermediate 14) in the preparation of N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide (Example 52). It was obtained as a white solid (5%) via recrystallisation from acetonitrile. HRMS calculated for $C_{19}H_{20}Cl_2N_4O_2$ (M+H)⁺ 407.1042, found: 407.1022, Rt: 2.40 min. MP: 120°C.

The following compounds were similarly prepared by analogous method to that described for Example 49:

Table 20

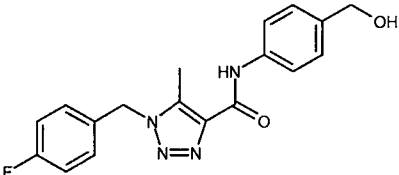
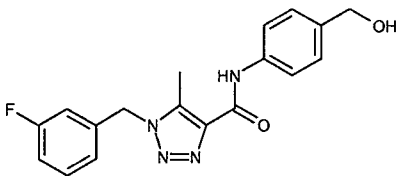
Compound	Structure	From	Physical data
Example 80 N-[3,4-bis(Hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide		dimethyl 4-([5-methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl]carbonyl)amino)-1,2-benzenedicarboxylate (Intermediate 20)	HRMS calculated for $C_{19}H_{20}N_4O_3$ Theo : 353.1613 Found: 353.1593 Rt: 2.23 min. MP: 171.4°C

Compound	Structure	From	Physical data
Example 81 N-[3,5-bis(Hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		dimethyl 5-[(1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,3-benzene dicarboxylate (Intermediate 21)	HRMS calculated for $C_{19}H_{19}FN_4O_3$ Theo : 371.1519 Found: 371.1537 Rt: 2.22 min. MP: 180.3°C
Example 82 N-[3,4-bis(Hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		dimethyl 4-[(1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,2-benzene dicarboxylate (Intermediate 22)	HRMS calculated for $C_{19}H_{19}ClN_4O_3$ Theo : 387.1224 Found: 387.1223 Rt: 2.41 min. MP: 157°C
Example 83 N-[3,4-bis(Hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		dimethyl 4-[(1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,2-benzene dicarboxylate (Intermediate 23)	HRMS calculated for $C_{19}H_{19}FN_4O_3$ Theo : 371.1519 Found: 371.1544 Rt: 2.29 min. MP: 175.5°C
Example 84 N-[3,5-bis(Hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		dimethyl 5-[(1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,3-benzene dicarboxylate (Intermediate 27)	HRMS calculated for $C_{19}H_{19}FN_4O_3$ Theo : 369.1363 Found: 369.1342 Rt: 2.20 min. MP: 173.1°C
Example 85 N-[3,4-bis(Hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		dimethyl 5-[(1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,3-benzene dicarboxylate (Intermediate 28)	HRMS calculated for $C_{19}H_{19}FN_4O_3$ Theo : 371.1519 Found: 371.1533 Rt: 2.15 min. MP: 157.2°C

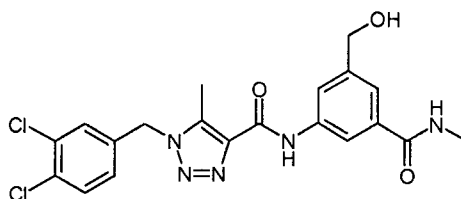
The following compounds were similarly prepared by analogous method to that described for Example 1:

Table 21

Compound	Structure	From	Physical data
Example 86 1-[(3-Chlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 13) and (3-aminophenyl) methanol	HRMS calculated for C ₁₈ H ₁₇ ClN ₄ O ₂ Theo: 355.0962 Found: 355.0927 Rt: 2.64 min MP: 151.9°C
Example 87 1-[(4-Fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and (3-aminophenyl) methanol	HRMS calculated for C ₁₈ H ₁₇ FN ₄ O ₂ Theo: 339.1257 Found: 339.1264 Rt: 2.67 min MP: 142.1°C
Example 88 1-[(3-Chlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 13) and (4-aminophenyl) methanol	HRMS calculated for C ₁₈ H ₁₇ ClN ₄ O ₂ Theo: 357.1118 Found: 357.1109 Rt: 2.74 min MP: 136.2°C
Example 89 1-[(3-Fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 26) and (3-aminophenyl) methanol	HRMS calculated for C ₁₈ H ₁₇ FN ₄ O ₂ (M-H) ⁺ Theo: 339.1257 Found: 339.1272 Rt: 2.64 min MP: 124.7°C

Compound	Structure	From	Physical data
Example 90 1-[(4-Fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid and (4-aminophenyl) methanol	HRMS calculated for $C_{18}H_{17}FN_4O_2$ Theo: 341.1414 Found: 341.1434 Rt: 2.61 min MP: 145.6°C
Example 91 1-[(3-Fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide		1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Intermediate 26) and (4-aminophenyl) methanol	HRMS calculated for $C_{18}H_{17}FN_4O_2$ Theo: 341.1414 Found: 341.1427 Rt: 2.57 min MP: 134.3°C

Example 92: 1-[(3,4-Dichlorophenyl)methyl]-N-{3-(hydroxymethyl)-5-[(methylamino)carbonyl]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide



5

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To a solution of methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-5-[(methylamino)carbonyl]benzoate (intermediate 31) (0.206 g, 0.43 mmol) in THF (5 mL), was added a 1M solution of $LiAlH_4$ in THF (0.65 mL, 1.5 eq.). The reaction was stirred at RT for one night. Water was added and the compound was extracted with AcOEt, dried over sodium sulfate and concentrated in vacuo. After trituration from hot methanol, filtration and dry, the title compound was obtained as a white solid (0.03 g, 15.8%). HRMS calculated for $C_{20}H_{19}Cl_2N_5O_3$ ($M+H$)⁺ 448.0943, found: 448.0910, Rt: 2.66 min. MP: 223-225°C.

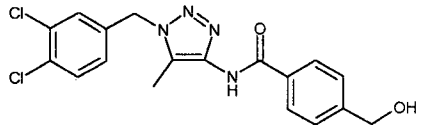
15

The following compound was similarly prepared by analogous method to that described for Example 49:

20

Table 22

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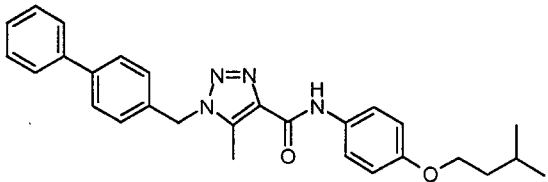
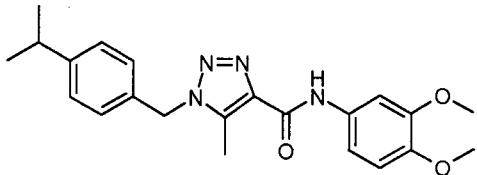
Compound	Structure	From	Physical data
Example 93 N-{1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}-4-(hydroxymethyl)benzamide		methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)amino]carbonyl benzoate (Intermediate 34)	HRMS calculated for C ₁₈ H ₁₆ Cl ₂ N ₄ O ₂ Theo : 391.0728 Found: 391.0740 Rt: 2.47 min. MP: 160°C

5 **BIOLOGICAL ASSAY**

The compounds of the present invention may be analysed *in vitro* for SCD activity using an assay based on the production of [³H]H₂O, which is released during the enzyme-catalyzed generation of the monounsaturated fatty acyl CoA product. The assay is performed in a 96-well filtration plates. The titrated substrate used in the assay is the [9,10-³H] stearoyl Coenzyme A. After incubation for 6 minutes of SCD-containing rat microsomes (2 µg protein) and substrate (1 µM), the labelled fatty acid acyl-CoA species and microsomes are absorbed with charcoal and separated from [³H]H₂O by centrifugation. The formation of [³H]H₂O is used as a measure of SCD activity. Compounds at concentrations starting at 10 µM to 0.1 nM or vehicle (DMSO) are preincubated for 5 minutes with the microsomes before addition of the substrate. The concentration-responses are fitted with sigmoidal curves to obtain IC₅₀ values.

All of the synthetic Example compounds 1-93 tested by the above described *in vitro* assay for SCD activity were found to exhibit an average pIC₅₀ value of greater than 5.5.

The following compounds were also prepared and when tested by the above described *in vitro* assay for SCD activity were found to exhibit an average pIC₅₀ value of less than 5.

Name	Structure
1-(4-Biphenylmethyl)-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide	
N-[3,4-Bis(methoxy)phenyl]-5-methyl-1-[[4-(1-methylethyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide	

83

Methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-(methoxy)benzoate	
Dimethyl 5-[(5-methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-benzenedicarboxylate	
Dimethyl 5-[(1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-benzenedicarboxylate	
5-[(1-[(3-Chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-benzenedicarboxylic acid	
Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-methylbenzoate	
Dimethyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-benzenedicarboxylate	
5-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-N,N'-dimethyl-1,3-benzenedicarboxamide	

SM

Dimethyl 4-({[5-methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl]carbonyl}amino)-1,2-benzenedicarboxylate	
Dimethyl 5-[(1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl)amino]-1,3-benzenedicarboxylate	
1-[(3,4-dichlorophenyl)methyl]-5-methyl-N-{2-methyl-3-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide	

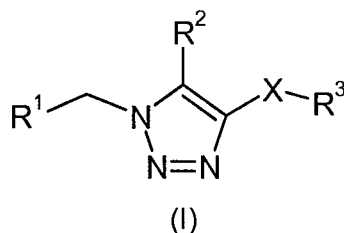
The following compounds were also prepared and when tested by the above described *in vitro* assay for SCD activity were found to exhibit an average pIC₅₀ value of between 5 and 5.5.

5

Name	Structure
1-[(4-fluorophenyl)methyl]-5-methyl-N-(5,6,7,8-tetrahydro-2-naphthalenyl)-1H-1,2,3-triazole-4-carboxamide	

Claims

1. A compound of formula (I):



wherein:

10 X represents -CONH-, -NHCO- or -CH₂NH-;

R¹ represents:

-C₆₋₁₀aryl optionally substituted by one, two or three groups independently selected from:

- 15 (a) -C₁₋₆alkyl, -OCH₃, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen;
- (b) phenyl optionally substituted by one, two or three groups independently selected from: halogen;

R² represents hydrogen or -C₁₋₆alkyl;

20

R³ represents:

-C₆₋₁₀aryl optionally substituted by one, two or three groups independently selected from:

- 25 (a) -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkoxy, -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, -C₀₋₆alkylOH, -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen;
- (b) -C₅heteroaryl;

30 R⁴ represents -C₆₋₁₀aryl;

R⁵ represents -H or -C₁₋₆alkyl;

R⁶ represents -H or -C₁₋₃alkyl or -C₁₋₃alkylOH;

R⁷ represents -H or -C₁₋₃alkyl;

R⁸ represents -H or -C₁₋₃alkyl;

R⁹ represents -H or -C₁₋₃alkyl;

35

m represents 1-3;

n represents 0-3;

p represents 0-3; and

q represents 1-3;

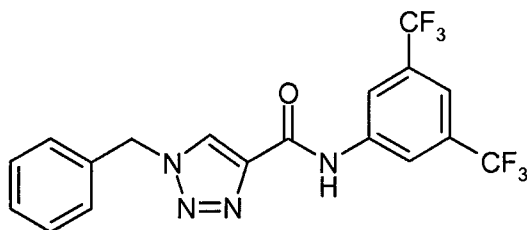
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or a pharmaceutically acceptable salt thereof;

with the proviso that the compound of formula (I) is not

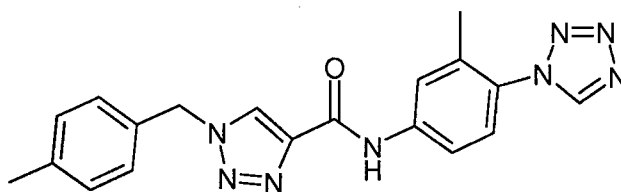
N-[3,5-bis(trifluoromethyl)phenyl]-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,

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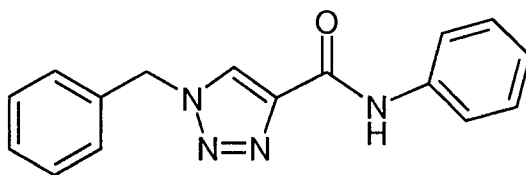
N-[2-(5-methyl-2-furanyl)phenyl]-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,

10



or, N-phenyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,

15



2. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 wherein X represents -CONH- or -CH₂NH-.

20 3. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 or claim 2 wherein R¹ represents phenyl optionally substituted by one, two or three groups independently selected from:

- (a) -C₁₋₆alkyl, -OCH₃, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl, or halogen;
- 25 (b) phenyl optionally substituted by one, two or three groups independently selected from: halogen.

4. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 3 wherein R² represents hydrogen or -C₁₋₃alkyl.

30

5. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 wherein R³ represents phenyl optionally substituted by one, two or three groups independently selected from:
- (a) -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkoxy, -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, -C₀₋₆alkylOH, -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen;
- (b) -C₅heteroaryl.
6. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 wherein R³ represents phenyl optionally substituted by:
- (i) one group independently selected from -(CH₂)_nCO₂R⁵ or -C(=O)NHR⁶ and/or,
- (ii) one, two or three groups independently selected from:
- (a) -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkoxy, -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nOC(=O)R⁵, -C₀₋₆alkylOH, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen;
- (b) -C₅heteroaryl.
7. A compound of formula (I) according to claim 1 selected from:
- N-[3,4-bis(methoxy)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- N-[3,4-bis(methoxy)phenyl]-1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 5-Methyl-1-(phenylmethyl)-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
- 1-[(2'-Chloro-4-biphenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
- 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[4-(1-methylethyl)phenyl]methyl-1H-1,2,3-triazole-4-carboxamide,

- N-[3,4-Bis(methyloxy)phenyl]-5-methyl-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
1-(2-Biphenylmethyl)-N-[3,4-bis(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 5 N-[3,4-Bis(methyloxy)phenyl]-1-[(4-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1,3-oxazol-2-yl)phenyl]-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 10 Methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-3-(methyloxy)benzoate,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{3-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-{4-[(methylamino)carbonyl]phenyl}-1H-1,2,3-triazole-4-carboxamide,
- 15 Ethyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate,
N-[3-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 20 N-[4-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 25 Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-hydroxy-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 30 Ethyl {4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}acetate,
Methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-(methyloxy)benzoate,
Methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-hydroxybenzoate,
- 35 Methyl {3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}acetate,
1-[(3,4-Dichlorophenyl)methyl]-N-(3-hydroxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 40 Methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-fluorobenzoate,
N-[5-(Aminocarbonyl)-2-(methyloxy)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,

- Methyl 4-chloro-3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate,
Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)phenyl]acetate,
5 Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-fluorobenzoate,
N-[3-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[4-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-
10 carboxamide,
1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 3-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)benzoate,
15 1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3-(Acetylamino)methyl]phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-
20 carboxamide,
N-[4-chloro-3-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Dimethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-1,2-benzenedicarboxylate,
25 Methyl 5-[(1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-fluorobenzoate,
Ethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-
30 1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
35 N-[3,5-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[5-(2-hydroxyethyl)-2-(methyloxy)phenyl]-5-methyl-1H-
40 1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[2-fluoro-5-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,

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- N-[2-chloro-5-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,5-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 5 N-[3,4-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,5-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-
- 10 carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 15 3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoic acid,
3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)benzoic acid,
5-[(5-Methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl)carbonyl]amino)-1,3-
- 20 benzenedicarboxylic acid,
4-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoic acid,
1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(ethylamino)carbonyl]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 25 1-[(3,4-Dichlorophenyl)methyl]-N-(3-[(2-hydroxyethyl)amino]carbonyl)phenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[5-[(methylamino)carbonyl]-2-(methyloxy)phenyl]-1H-1,2,3-triazole-4-carboxamide,
{3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-
- 30 yl)carbonyl]amino]phenyl}methyl acetate,
{3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}methyl acetate,
{3-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}methyl benzoate,
- 35 {3-[(1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl}methyl benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-{4-[(2-hydroxyethyl)oxy]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1-methylethenyl)-2-(methyloxy)phenyl]-1H-
- 40 1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxy-1-methylethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,

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- 1-[(3,4-Dichlorophenyl)methyl]-N-[4-{[2-(dimethylamino)ethyl]oxy}-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3,4-Dichlorophenyl)methyl]-N-{3-[(2-hydroxyethyl)oxy]phenyl}-5-methyl-1H-1,2,3-triazole-4-carboxamide, and
- 5 {5-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)methyl]amino]benzene-1,3-diyl}dimethanol, or a pharmaceutically acceptable salt thereof.

8. A compound of formula (I) according to claim 1 selected from:
- 10 N-[3,4-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide, N-[3,5-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-
- 15 carboxamide, N-[3,4-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 20 N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3-chlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(4-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-
- 25 carboxamide, 1-[(3-chlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide
- 30 1-[(4-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, 1-[(3-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
- 35 1-[(3,4-dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-5-[(methylamino)carbonyl]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, and N-{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}-4-(hydroxymethyl)benzamide or a pharmaceutically acceptable salt thereof.

- 40 9. A compound of formula (I) according to claim 1 which is N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 together with at least one pharmaceutical carrier and/or excipient.

5 11. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for use in therapy.

12. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for the manufacture of a medicament for treating
10 and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

13. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 12 for the manufacture of a medicament for treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile
15 including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension,
20 vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and
25 the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42.

30 14. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 12 for the manufacture of a medicament for treating and/or preventing acne, psoriasis, skin ageing, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

35 15. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 12 for the manufacture of a medicament for treating and/or preventing acne.

40 16. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for use in treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

17. A compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 16 for use in treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42.

18. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 16 for use in treating and/or preventing acne, psoriasis, skin ageing, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

19. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 16 for use in treating and/or preventing acne.

20. A method of treating and/or preventing a disease or a condition susceptible to amelioration by an SCD comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 9.

21. A method of treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive

impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42 comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 20.

22. A method of treating and/or preventing acne, psoriasis, skin ageing, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH) comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 20.

23. A method of treating and/or preventing acne, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 20.

24. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 in combination with one or more active agent(s) selected from an inhibitor of cholesteryl ester transferase (CETP inhibitors), a HMG-CoA reductase inhibitor, a microsomal triglyceride transfer protein, a peroxisome proliferator-activated receptor activator (PPAR), a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an inhibitor of AcylCoA: cholesterol acyltransferase (ACAT inhibitor), a cannabinoid 1 antagonist and a bile acid sequestrant.

25. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 in combination with one or more active agent(s) selected from a corticosteroid, a vitamin D3 derivative, a retinoid, an immunomodulator, an anti androgen, a keratolytic agent, an anti-microbial, a platinum chemotherapeutic, an antimetabolite, hydroxyurea, a taxane, a mitotic disrupter, an anthracycline, dactinomycin, an alkylating agent and a cholinesterase inhibitor.

DERIVADOS DE 1, 2, 3-TRIAZOL PARA USO COMO INHIBIDORES DE
ESTEAROIL-COENZIMA A DESATURASA

CAMPO DE LA INVENCION

5

La presente invención se relaciona con una clase novedosa de compuestos que se cree son inhibidores de estearoil-CoA desaturasa (SCD), composiciones que comprenden dichos compuestos, métodos de síntesis y usos para tales compuestos para tratar y/o prevenir diversas enfermedades, incluyendo aquellas mediadas por la enzima SCD, como enfermedades relacionadas con niveles elevados de lípidos, enfermedad cardiovascular, diabetes, obesidad, síndrome metabólico, trastornos de la piel como acné, enfermedades o condiciones relacionadas con cáncer y el tratamiento de síntomas vinculados a la producción del péptido A β 42 formador de placa amiloide, como la enfermedad de Alzheimer y similares.

15

ANTECEDENTES DE LA INVENCION

Las enzimas de acil desaturasa catalizan la formación de enlaces dobles en ácidos grasos derivados de fuentes dietéticas o síntesis *de novo* en el hígado. Los mamíferos sintetizan al menos tres ácidos grasos desaturadas de diferente longitud de cadena que catalizan específicamente la adición de enlaces dobles en las posiciones delta-9, delta-6 y delta-5. Las

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estearoil-CoA desaturasas (SCD) introducen un enlace doble en la posición C9-C10 de los ácidos grasos saturados. Los sustratos preferidos para las enzimas son palmitoil-CoA (16:0) y estearoil-CoA (18:0), que se convierten a palmitoleoil-CoA (16:1) y a oleoil-CoA (18:1), respectivamente. Los ácidos
5 grasos monoinsaturados resultantes pueden emplearse en la preparación de fosfolípidos, triglicéridos y ésteres colestéricos, *in vivo*.

Se han clonado una serie de genes de SCD de mamífero. Por ejemplo, se han clonado dos genes a partir de ratas (SCD1, SCD2) y cuatro genes de SCD se han aislado de ratones (SCD1, 2, 3 y 4). Aunque se conoce
10 desde la década de los 70 los roles bioquímicos básicos de la SCD en ratones y ratas (Jeffcoat, R *et al.*, *Elsevier Science* (1984), Vol 4, pp. 85-112; de Antueno, RJ, *Lipids* (1993), Vol. 28, No. 4, pp. 285-290), sólo recientemente se ha implicado directamente con procesos de enfermedades en humanos.

Un gen de SCD en particular, SCD1, se ha caracterizado en
15 humanos. SCD1 se describe en Brownlie *et al*, WO 01/62954. Se ha identificado una segunda isoforma de SCD de humano y ya que tiene escasa homología en secuencias con las isoformas conocidas de ratón o rata se ha denominado como SCD5 o hSCD5 de humano (WO 02/26944).

Aunque no se desea estar limitado a teoría laguna, se piensa
20 que la inhibición de la actividad de SCD *in vivo* puede usarse para mejorar y/o tratar una o más enfermedades como dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, apoplejía,

infarto al miocardio, aterosclerosis, obesidad, diabetes tipo I, diabetes tipo II, resistencia a insulina, hiperinsulinemia, síndrome metabólico; otras enfermedades cardiovasculares por ejemplo enfermedad vascular periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones

5 vasculares de la diabetes, trombosis; esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras enfermedades relacionadas con la acumulación de lípidos en el hígado.

Una enfermedad o condición mediada por SCD también incluye un trastorno por ácido graso poliinsaturado (PUFA), o un trastorno de la piel,

10 incluyendo sin restricción eczema, acné, psoriasis, formación o prevención de cicatrices queloides, enfermedades relacionadas con la producción de o secreciones de membranas mucosas, como ácidos grasos monoinsaturados, ésteres de cera y similares (US2006/0205713A1, WO2007/046868, WO2007/046867). Se ha mostrado que SCD juega un rol fisiológico en la

15 homeóstasis del colesterol y en la síntesis de novo de ésteres de colesterol, triglicéridos y ésteres de cera requeridos para la función normal de la piel y párpados y por ello pueden ser útiles en el tratamiento de acné y de otras condiciones de la piel (Makoto et al. J of Nutrition (2001), 131(9), 2260-2268, Harrison et al. J of Investigative Dermatology (2007) 127(6), 1309-1317).

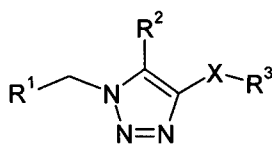
20 Una enfermedad o condición mediada por SCD también incluye sin restricción pero no se limita a una enfermedad o condición que es, o se relaciona con, cáncer, neoplasia, tumor maligno, metástasis, tumores (benignos o malignos), carcinogénesis, hepatomas y similares

(US2006/0205713A1, WO2007/046868, WO2007/046867). Recientemente se ha identificado a SCD-1 como con un rol en la supervivencia celular en tumores humanos y por ello tiene potencial como una diana anticáncer (Morgan-Lappe et al. 2007 Cancer Res. 67(9) 4390-4398).

5 Se ha mostrado que la sobreexpresión de la esteroil-CoA desaturasa (SCD) en células humanas en cultivos lleva a un incremento específico en la producción del péptido A β 42 formado de placa amiloide y, por el contrario, que las reducciones en la actividad de SCD en células humanas en cultivo lleva a a una disminución específica en la producción de A β 42. Por
10 ello, los inhibidores de SCD también pueden ser útiles para tratar, demorar el inicio de síntomas o desacelerar el avance de síntomas del deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloide cerebral (CAA) o demencia asociada con el síndrome de Down (DS) y otras enfermedades neurodegenerativas caracterizadas por la formación o
15 acumulación de placas amiloides que comprenden A β 42 (US2007/0087363A1; Myriad Genetics).

WO2005/011657 describe ciertos derivados de piperazina útiles para inhibir la actividad de SCD.

La presente invención proporciona un compuesto de fórmula (I) para inhibir la
20 actividad de SCD:



(I)

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en donde:

X representa -CONH-, -NHCO- o -CH₂NH-;

R¹ representa:

arilo de C₆₋₁₀ (como fenilo) opcionalmente sustituido por uno, dos

5 o tres grupos seleccionados independientemente de:

(a) alquilo de C₁₋₆ (como -CH₃, o -CH(CH₃)₂), -OCH₃, haloalquilo de C₁₋₆ (como -CF₃), haloalquilo de OC₁₋₆ (como -OCF₃), cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno (como cloro, bromo o fluoro);

10 (b) fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: halógeno (como cloro, bromo o fluoro);

R² representa hidrógeno o alquilo de C₁₋₆ (como -CH₃);

R³ representa:

arilo de C₆₋₁₀ (como fenilo) opcionalmente sustituido por uno, dos

15 o tres grupos seleccionados independientemente de:

(a) alquilo de C₁₋₆ (como -CH₃), alquenilo de C₁₋₆, alcoxi de C₁₋₆ (como -OCH₃ o -OC₂H₄CH(CH₃)₂), -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, alquilo C₀₋₆OH (como -CH₂OH, -C(CH₃)₂OH o -CH(CH₃)OH), -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, alquilo OC₁₋₆OH, haloalquilo de C₁₋₆ (como -CF₃), haloalquilo de OC₁₋₆ (como -OCF₃), cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno (como cloro, bromo o fluoro);

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(b) heteroarilo de C₅ (como oxazol);

(100)

R^4 representa arilo de C_{6-10} (como fenilo);

R^5 representa -H o alquilo de C_{1-6} (como $-CH_3$);

R^6 representa -H o alquilo de C_{1-3} (como $-CH_3$) o alquilo $C_{1-3}OH$;

R^7 representa -H o alquilo de C_{1-3} (como $-CH_3$);

5 R^8 representa -H o alquilo de C_{1-3} (como $-CH_3$);

R^9 representa -H o alquilo de C_{1-3} (como $-CH_3$);

m representa 1-3;

n representa 0-3;

p representa 0-3; y

10 q representa 1-3;

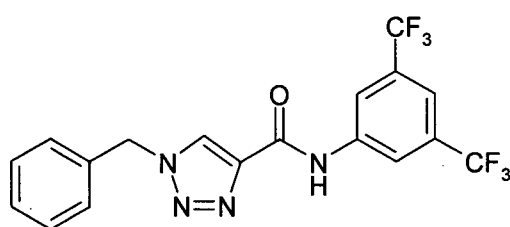
o una sal farmacéuticamente aceptable del mismo;

con la condición de que el compuesto de fórmula (I) no sea

N-[3,5-bis(trifluorometil)fenil]-1-(fenilmetil)-1H-1,2,3-triazol-4-

carboxamida,

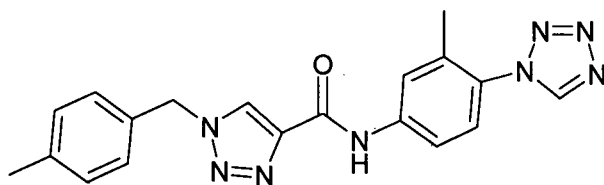
15



N-[2-(5-metil-2-furanil)fenil]-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-

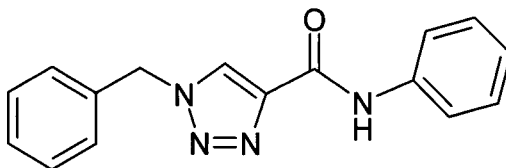
4-carboxamida,

20



CO

o, N-fenil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida.



- 5 Se ha encontrado que dichos compuestos inhiben la actividad de SCD y por ello pueden ser útiles en el tratamiento de enfermedades mediadas por SCD como enfermedades o condiciones causadas o asociadas con un perfil anormal de lípidos en plasma, incluyendo dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, apoplejía, infarto al miocardio, aterosclerosis, obesidad, diabetes tipo I, diabetes tipo II, resistencia a insulina, hiperinsulinemia y síndrome metabólico; otras enfermedades cardiovasculares por ejemplo enfermedad vascular periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de la diabetes, trombosis; esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras enfermedades relacionadas con la acumulación de lípidos en el hígado; trastornos de la piel por ejemplo eczema, acné, psoriasis, formación o prevención de cicatrices queloides, enfermedades relacionadas con la producción de o secreciones de membranas mucosas; cáncer, neoplasia, tumor maligno, metástasis, tumores (benignos o malignos), carcinogénesis, hepatomas y similares; deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloide cerebral (CAA) o demencia asociada con el síndrome de Down (DS) y otras
- 10
- 15
- 20

02

enfermedades neurodegenerativas caracterizadas por la formación o acumulación de placas amiloides que comprenden A β 42.

En un aspecto de la invención X representa -CONH-. En otro aspecto de la invención, X representa -NHCO-. En otro aspecto de la invención, X representa -CH₂NH-. En otros aspecto de la invención, X representa -CONH- o -CH₂NH-.

En un aspecto de la invención, R¹ representa fenilo sustituido por uno, dos o tres grupos seleccionados independientemente de:

(a) alquilo de C₁₋₆ (como -CH₃ o -CH(CH₃)₂), -OCH₃, haloalquilo de C₁₋₆ (como -CF₃), haloalquilo de OC₁₋₆ (como -OCF₃), cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno (como cloro, bromo o fluoro),

(b) fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R¹ representa fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de:

(a) alquilo de C₁₋₆ (como -CH₃, -CH(CH₃)₂), -OCH₃, haloalquilo de C₁₋₆ (como -CF₃), haloalquilo de OC₁₋₆ (como -OCF₃), cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno (como cloro, bromo o fluoro);

(b) fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R¹ representa fenilo opcionalmente sustituido por uno o dos grupos seleccionados

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independientemente de: alquilo de C_{1-6} (como $-CH_3$ o $-CH(CH_3)_2$), $-OCH_3$, haloalquilo de C_{1-6} (como $-CF_3$), haloalquilo de OC_{1-6} (como $-OCF_3$), cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno (como cloro, bromo o fluoro), o fenilo opcionalmente sustituido por uno o dos grupos seleccionados

5 de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: alquilo de C_{1-3} (como $-CH_3$ o $-CH(CH_3)_2$), $-OCH_3$, haloalquilo de C_{1-3} (como $-CF_3$), haloalquilo de OC_{1-3} (como $-OCF_3$),

10 cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno (como cloro, bromo o fluoro), o fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno o dos grupos seleccionados independientemente de: alquilo de C_{1-3} (como $-CH_3$ o $-CH(CH_3)_2$), $-OCH_3$, haloalquilo de C_{1-3} (como $-CF_3$), haloalquilo de OC_{1-3} (como $-OCF_3$),

15 cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno (como cloro, bromo o fluoro), o fenilo opcionalmente sustituido por uno o dos grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

20 En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: alquilo de C_{1-6} (como $-CH_3$ o $-CH(CH_3)_2$) o halógeno (como cloro, bromo o fluoro) o fenilo opcionalmente sustituido por uno, dos o

tres grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno o dos grupos seleccionados independientemente de: alquilo de C_{1-6} (como $-CH_3$ o $-CH(CH_3)_2$) o halógeno
5 (como cloro, bromo o fluoro) o fenilo opcionalmente sustituido por uno o dos grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: alquilo de C_{1-3} (como $-CH_3$ o $-CH(CH_3)_2$) o halógeno
10 (como cloro, bromo o fluoro) o fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno o dos grupos seleccionados independientemente de: alquilo de C_{1-3} (como $-CH_3$ o $-CH(CH_3)_2$) o halógeno
15 (como cloro, bromo o fluoro) o fenilo opcionalmente sustituido por uno o dos grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: $-CH_3$, $-CH(CH_3)_2$ o halógeno (como cloro, bromo o
20 fluoro) o fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo opcionalmente sustituido por uno o dos grupos seleccionados

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independientemente de: $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$ o halógeno (como cloro, bromo o fluoro) o fenilo opcionalmente sustituido por uno o dos grupos seleccionados de: halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo sustituido por dos grupos seleccionados independientemente de halógeno (como cloro, bromo o fluoro).

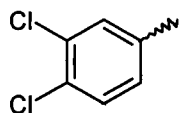
En otro aspecto de la invención, R^1 representa fenilo sustituido por un grupo seleccionado independientemente de halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo sustituido por fenilo opcionalmente sustituido por halógeno (como cloro, bromo o fluoro).

En otro aspecto de la invención, R^1 representa fenilo sustituido por fenilo.

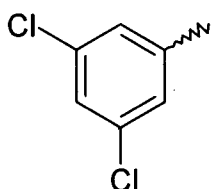
En otro aspecto de la invención, R^1 representa fenilo sustituido por dos grupos cloro.

En otros aspecto de la invención, R^1 es fenilo sustituido en la posición meta, es decir en la posición 3, y la posición para, es decir en la posición 4, mediante halógeno, por ejemplo cloro es decir



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En otro aspecto de la invención, R^1 es fenilo sustituido en la posición meta, es decir en la posición 3 y la posición 5, mediante halógeno, por ejemplo cloro es decir



En otro aspecto de la invención, R^1 es fenilo.

5 En un aspecto de la invención, R^2 representa hidrógeno. En otro aspecto de la invención, R^2 representa alquilo de C_{1-6} . En otro aspecto de la invención, R^2 representa alquilo de C_{1-3} . En otro aspecto de la invención, R^2 representa $-CH_3$ (metilo). En otro aspecto de la invención, R^2 representa hidrógeno o alquilo de C_{1-3} .

10 En un aspecto de la invención, R^3 representa fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de:

(a) alquilo de C_{1-6} (como $-CH_3$), alqueno de C_{1-6} , alcoxi de C_{1-6} (como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$ (como $-CH_2OH$, $-C(CH_3)_2OH$ o $-CH(CH_3)OH$), $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo de C_{1-6} (como $-CF_3$), haloalquilo de OC_{1-6} (como $-OCF_3$), cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno (como cloro, bromo o fluoro),

20 (b) heteroarilo de C_5 (como oxazol).

En otro aspecto de la invención, R^3 representa fenilo opcionalmente sustituido por uno o dos grupos seleccionados independientemente de:

(a) alquilo de C_{1-6} (como $-CH_3$), alqueno de C_{1-6} , alcoxi de C_{1-6} (como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$ (como $-CH_2OH$, $-C(CH_3)_2OH$ o $-CH(CH_3)OH$), $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo de C_{1-6} (como $-CF_3$), haloalquilo de OC_{1-6} (como $-OCF_3$), cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno (como cloro, bromo o fluoro),

(b) heteroarilo de C_5 (como oxazol).

En otro aspecto de la invención, R^3 representa fenilo
10 opcionalmente sustituido por:

(i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$ o $-C(=O)NHR^6$ y/o,

(ii) uno, dos o tres grupos seleccionados independientemente de:

15 (a) alquilo de C_{1-6} (como $-CH_3$), alqueno de C_{1-6} , alcoxi de C_{1-6} (como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$ (como $-CH_2OH$, $-C(CH_3)_2OH$ o $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo C_{1-6} (como $-CF_3$), haloalquilo de OC_{1-6} (como $-OCF_3$), cicloalquilo de C_{3-6} , cicloalquilo de
20 OC_{3-6} o halógeno (como cloro, bromo o fluoro),

(b) heteroarilo de C_5 (como oxazol).

En otro aspecto de la invención, R^3 representa fenilo
opcionalmente sustituido por:

(i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$
o $-C(=O)NHR^6$ y/o,

(ii) uno o dos grupos seleccionados independientemente de:

- (a) alquilo de C_{1-6} (como $-CH_3$), alqueno de C_{1-6} , alcoxi de C_{1-6}
5 (como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$ (como $-CH_2OH$, $-C(CH_3)_2OH$ o $-CH(CH_3)OH$),
 $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo C_{1-6} (como $-CF_3$), haloalquilo de OC_{1-6} (como $-OCF_3$), cicloalquilo de C_{3-6} , cicloalquilo de
 OC_{3-6} o halógeno (como cloro, bromo o fluoro),
10 (b) heteroarilo de C_5 (como oxazol).

En otro aspecto de la invención, R^3 representa fenilo
opcionalmente sustituido por:

(i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$
o $-C(=O)NHR^6$ y/o,

- 15 (ii) uno, dos o tres grupos seleccionados independientemente
de:

- (a) alquilo de C_{1-3} (como $-CH_3$), alqueno de C_{1-3} , alcoxi de C_{1-6}
(como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-3}OH$ (como $-CH_2OH$, $-C(CH_3)_2OH$ o $-CH(CH_3)OH$),
20 $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo C_{1-3} (como $-CF_3$), haloalquilo de OC_{1-3} (como $-OCF_3$), cicloalquilo de C_{3-6} , cicloalquilo de
 OC_{3-6} o halógeno (como cloro, bromo o fluoro),

(b) heteroarilo de C_5 (como oxazol).

En otro aspecto de la invención, R^3 representa fenilo opcionalmente sustituido por:

(i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$ o $-C(=O)NHR^6$ y/o,

5 (ii) uno o dos grupos seleccionados independientemente de:

(a) alquilo de C_{1-3} (como $-CH_3$), alquenilo de C_{1-3} , alcoxi de C_{1-6} (como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-3}OH$ (como $-CH_2OH$, $-C(CH_3)_2OH$ o $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo C_{1-3} (como $-CF_3$), haloalquilo de OC_{1-3} (como $-OCF_3$), cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno (como cloro, bromo o fluoro),

10

(b) heteroarilo de C_5 (como oxazol).

En otro aspecto de la invención, R^3 representa fenilo opcionalmente sustituido por:

15 (i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$ o $-C(=O)NHR^6$ y/o,

(ii) uno, dos o tres grupos seleccionados independientemente de:

(a) alquilo de C_{1-3} (como $-CH_3$), alquenilo de C_{1-3} , alcoxi de C_{1-6} (como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-3}OH$ (como $-CH_2OH$, $-CH(CH_3)_2OH$ o $-CH(CH_3)OH$), $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$ o halógeno (como cloro, bromo o fluoro),

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(b) heteroarilo de C₅ (como oxazol).

En otro aspecto de la invención, R³ representa fenilo opcionalmente sustituido por:

(i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$

5 o $-C(=O)NHR^6$ y/o,

(ii) uno o dos grupos seleccionados independientemente de:

(a) alquilo de C₁₋₃ (como $-CH_3$), alqueno de C₁₋₃, alcoxi de C₁₋₆

(como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, -

$(CH_2)_nOC(=O)R^5$, alquilo C₀₋₃OH (como $-CH_2OH$, $-CH(CH_3)_2OH$ o -

10 $CH(CH_3)OH$) $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo OC₁₋₆OH o halógeno

(como cloro, bromo o fluoro),

(b) heteroarilo de C₅ (como oxazol).

En otro aspecto de la invención, R³ representa fenilo opcionalmente sustituido por:

15 (i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$

o $-C(=O)NHR^6$ y/o,

(ii) uno, dos o tres grupos seleccionados independientemente

de:

(a) alquilo de C₁₋₃ (como $-CH_3$), alqueno de C₁₋₃, alcoxi de C₁₋₆

20 (como $-OCH_3$ o $-OC_2H_4CH(CH_3)_2$), $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, -

$(CH_2)_nOC(=O)R^5$, alquilo C₀₋₃OH (como $-CH_2OH$, $-CH(CH_3)_2OH$ o -

$CH(CH_3)OH$) $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo OC₁₋₆OH o halógeno

(como cloro, bromo o fluoro),

(b) oxazol.

En otro aspecto de la invención, R^3 representa fenilo opcionalmente sustituido por:

(i) un grupo seleccionado independientemente de $-CO_2H$, -
 5 CO_2CH_3 , $-CO_2C_2H_5$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-C(=O)NH_2$, $-C(=O)NHCH_3$,
 $-C(=O)NHC_2H_5$ o $-C(=O)NHC_2H_4OH$ y/o,

(ii) uno, dos o tres grupos seleccionados independientemente de:

(a) $-CH_3$, $-C(=CH_2)CH_3$, $-OCH_3$, $-OC_2H_4CH(CH_3)_2$, $-OCH_2R^4$, -
 10 $CH_2OC(=O)R^4$, $-CH_2OC(=O)CH_3$, $-CH_2OH$, $-C_2H_4OH$, $-CH(CH_3)OH$, -
 $C(CH_3)_2OH$, $-OH$, $-CH_2NHC(=O)CH_3$, $-NHC(=O)CH_3$, $-OC_2H_4N(CH_3)_2$, -
 OC_2H_4OH o halógeno (como cloro, bromo o fluoro),

(b) oxazol.

En otro aspecto de la invención, R^3 representa fenilo
 15 opcionalmente sustituido por:

(i) un grupo seleccionado independientemente de $-CO_2H$, -
 CO_2CH_3 , $-CO_2C_2H_5$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, -
 $C(=O)NHC_2H_5$ o $-C(=O)NHC_2H_4OH$ y/o,

(ii) uno o dos grupos seleccionados independientemente de:

(a) $-CH_3$, $-C(=CH_2)CH_3$, $-OCH_3$, $-OC_2H_4CH(CH_3)_2$, $-OCH_2R^4$, -
 20 $CH_2OC(=O)R^4$, $-CH_2OC(=O)CH_3$, $-CH_2OH$, $-C_2H_4OH$, $-CH(CH_3)OH$, -
 $C(CH_3)_2OH$, $-OH$, $-CH_2NHC(=O)CH_3$, $-NHC(=O)CH_3$, $-OC_2H_4N(CH_3)_2$, -
 OC_2H_4OH o halógeno (como cloro, bromo o fluoro),

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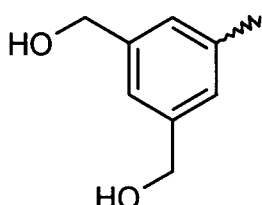
(b) oxazol.

En otro aspecto de la invención, R^3 representa fenilo opcionalmente sustituido por uno o dos grupos $-CH_2OH$.

En otro aspecto de la invención, R^3 representa fenilo sustituido
5 por uno o dos grupos $-CH_2OH$.

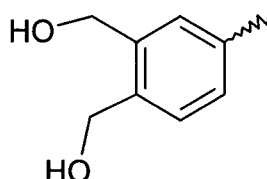
En otros aspecto de la invención, R^3 es fenilo sustituido en la posición meta, es decir en la posición 3 y la posición 5 por $-CH_2OH$ es decir

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En otros aspecto de la invención, R^1 es fenilo sustituido en la posición meta, es decir en la posición 3, y la posición para, es decir en la posición 4, por $-CH_2OH$ es decir

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En otro aspecto de la invención, R^3 representa fenilo sustituido por $-CH_2OH$.

20

En un aspecto de la invención, R^4 representa fenilo.

En un aspecto de la invención, R^5 representa hidrógeno. En otro aspecto de la invención, R^5 representa alquilo de C_{1-6} . En otro aspecto de la invención, R^5 representa alquilo de C_{1-3} . En otro aspecto de la invención, R^5

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representa $-C_2H_5$ (etilo). En otro aspecto de la invención, R^5 representa $-CH_3$ (metilo).

En un aspecto de la invención, R^6 representa hidrógeno. En otro aspecto de la invención, R^6 representa alquilo de C_{1-3} . En otro aspecto de la invención, R^6 representa $-C_2H_5$ (etilo). En otro aspecto de la invención, R^6 representa $-CH_3$ (metilo). En otro aspecto de la invención, R^6 representa alquilo $C_{1-3}OH$. En otro aspecto de la invención, R^6 representa $-C_2H_4OH$.

En un aspecto de la invención, R^7 representa hidrógeno. En otro aspecto de la invención, R^7 representa alquilo de C_{1-3} . En otro aspecto de la invención, R^7 representa $-CH_3$ (metilo).

En un aspecto de la invención, R^8 representa hidrógeno. En otro aspecto de la invención, R^8 representa alquilo de C_{1-3} . En otro aspecto de la invención, R^8 representa $-CH_3$ (metilo).

En un aspecto de la invención, R^9 representa hidrógeno. En otro aspecto de la invención, R^9 representa alquilo de C_{1-3} . En otro aspecto de la invención, R^9 representa $-CH_3$ (metilo).

En un aspecto de la invención m representa 1 ó 2. En otro aspecto de la invención, m representa 2. En otro aspecto de la invención, m representa 1.

En un aspecto de la invención n representa 0, 1 ó 2. En otro aspecto de la invención, n representa 3. En otro aspecto de la invención, n representa 2. En otro aspecto de la invención, n representa 1. En otro aspecto de la invención, n representa 0.

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En un aspecto de la invención p representa 0, 1 ó 2. En otro aspecto de la invención, p representa 2. En otro aspecto de la invención, p representa 1. En otro aspecto de la invención, p representa 0.

En un aspecto de la invención q representa 1 ó 2. En otro aspecto de la invención, q representa 2. En otro aspecto de la invención, q representa 1.

Cada uno de los aspectos de la invención son independientes a menos que se establezca lo contrario. No obstante el experto en la comprenderá que todas las permutaciones de los aspectos descritos están dentro del alcance de la invención. Así, debe entenderse que la presente invención abarca todas las combinaciones de grupos adecuados, convenientes y ejemplificados descritos aquí. Por ejemplo, en un aspecto la invención proporciona un compuesto de fórmula (I) en donde X representa -CONH- y R² representa -CH₃.

Ciertos compuestos de fórmula (I) pueden existir en formas estereoisoméricas (por ejemplo pueden contener uno o más átomos de carbono asimétricos). Los estereoisómeros individuales (enantiómeros y diaestereómeros) y mezclas de éstos se incluyen dentro del alcance de la presente invención. La invención también se extiende a isómeros conformacionales de los compuestos de fórmula (I) y cualesquier isómeros geométricos (*cis* y/o *trans*) de dichos compuestos. Igualmente, se entiende que los compuestos de fórmula (I) pueden existir en formas tautoméricas distintas a las mostradas en la fórmula y éstas también se incluyen dentro del

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alcance de la presente invención.

Se apreciará que los compuestos de fórmula (I) pueden resolverse opcionalmente en sus enantiómeros individuales. Tales resoluciones pueden lograrse convenientemente mediante métodos
5 estándares conocidos en la técnica. Por ejemplo, un compuesto racémico de fórmula (I) puede resolverse mediante HPLC preparativa quiral.

También se apreciará que los compuestos de la invención que existen como polimorfos, y mezclas de éstos, están dentro del alcance de la presente invención.

10 Como se utiliza aquí, el término "alquilo" se refiere a cadenas de hidrocarburo de cadena recta o ramificada que contiene el número especificado de átomos de carbono. Por ejemplo, alquilo de C_{1-6} significa un alquilo recto o ramificado que contiene al menos 1, y máximo 6, átomos de carbono. Ejemplos de alquilo como se utilizan aquí incluyen, sin restricción,
15 metilo, etilo, n-propilo, n-butilo, n-pentilo, n-hexilo, isobutilo, isopropilo, t-butilo y 1,1-dimetilpropilo. Sin embargo, cuando una porción se define de manera tal que el alquilo porta un sustituyente será claro para el experto en la técnica a partir del contexto que el alquilo puede incluir alquilenos, por ejemplo metileno ($-CH_2-$), etileno ($-CH_2CH_2-$) y propileno ($-CH_2CH_2CH_2-$).

20 Como se utiliza aquí, el término "alquiloOH" se refiere a cadenas de hidrocarburo de cadena recta o ramificada que contiene el número especificado de átomos de carbono y un grupo hidroxilo. Por ejemplo, alquilo $C_{1-6}OH$ significa un alquilo recto o ramificado que contiene al menos 1 y

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máximo 6 átomos de carbono y OH.

En un aspecto de la invención, el término "alquiloOH" se refiere a cadenas rectas de hidrocarburo que contienen el número especificado de átomos de carbono y un grupo hidroxilo. Por ejemplo, alquilo C₁₋₆OH significa un alquilo recto que contiene al menos 1 y máximo 6 átomos de carbono y OH. En un aspecto de la invención, la cadena alquilo en alquilo C₁₋₆OH es una cadena de hidrocarburo recta que contiene el número especificado de átomos de carbono y un grupo hidroxilo.

Como se utiliza aquí, el término "alqueno" se refiere a cadenas de hidrocarburo de cadena recta o ramificada que contienen el número especificado de átomos de carbono y uno o más enlaces dobles. Por ejemplo, alqueno de C₁₋₆ significa un alquilo recto o ramificado que contiene al menos 1 y máximo 6 átomos de carbono y al menos un enlace doble. Ejemplos de "alqueno" como se utilizan aquí incluyen, sin restricción, etenilo, 1-metiletlenilo, propil-2-eno, 2-propenilo, 3-butenilo, 2-butenilo, 2-pentenilo, 3-pentenilo, 3-metil-2-butenilo o 3-hexenilo.

Como se utiliza aquí, el término "alcoxi" se refiere a un grupo alcoxi de cadena recta o ramificada que contiene el número especificado de átomos de carbono. Por ejemplo, alcoxi de C₁₋₆ significa un grupo alcoxi recto o ramificado que contiene al menos 1, y máximo 6, átomos de carbono. Ejemplos de "alcoxi" como se utilizan aquí incluyen, sin restricción, metoxi, etoxi, propoxi, prop-2-oxi, butoxi, but-2-oxi, 2-metilprop-1-oxi, 2-metilprop-2-oxi, pentoxi y hexiloxi. El punto de unión puede ser en el átomo de oxígeno o

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carbono.

Como se utiliza aquí, el término "halógeno" o "halo" se refiere a un átomo de flúor (fluoro), cloro (cloro), bromo (bromo) o yodo (yodo).

Como se utiliza en la presente, el término "haloalquilo" se refiere a un grupo alquilo que tiene uno o más átomos de carbono y en donde al menos un átomo de hidrógeno se reemplaza con un átomo de halógeno, por ejemplo un grupo trifluorometilo y similares.

Como se utiliza en la presente, el término "cicloalquilo" se refiere a un grupo cíclico saturado que contiene 3 a 6 átomos de carbono en el anillo. Ejemplos incluyen ciclopropilo, ciclopentilo y ciclohexilo.

Como se utiliza aquí, el término "heteroarilio de C₅₋₁₀" se refiere a un grupo cíclico aromático que contiene 5 a 10 átomos en el anillo, 1, 2, 3 ó 4 de los cuales son heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre y los átomos en el anillo restantes son carbono, por ejemplo benzotiofenilo, indolilo o tienilo. Esta definición incluye sistemas de anillo tanto monocíclicos como bicíclicos y estructuras bicíclicas, al menos una porción de las cuales es aromática y la otra parte es saturada, parcial o totalmente insaturada.

Como se utiliza aquí, el término 'arilo' significa una porción carbocíclica aromática. la definición incluye sistemas de anillo tanto monocíclicos como bicíclicos y estructuras bicíclicas al menos una porción de las cuales es aromática y la otra parte es insaturada, parcial o completamente insaturada. Ejemplos de grupos arilo aromáticos incluyen naftilo, antrilo,

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fenantrilo, indanilo, indenilo, azulenilo, azulanilo, fluorenilo, fenilo y naftilo, y más específicamente fenilo.

Ejemplos de grupos heteroarilo incluyen: furilo, tienilo, pirrolilo, pirrolinilo, imidazolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, pirazolinilo, 5 isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo, tiadiazolilo, piranilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, sulfolanilo, tetrazolilo, triazinilo, azepinilo, oxazepinilo, tiazepinilo, diazepinilo y tiazolinilo, bencimidazolilo, benzoxazolilo, imidazopiridinilo, benzoxazinilo, benzotiazinilo, benzotiofenilo oxazolopiridinilo, benzofuranilo, quinolinilo, quinazolinilo, quinoxalinilo, dihidroquinazolinilo, 10 benzotiazolilo, ftalimido, benzofuranilo, benzodiazepinilo, indolilo e iscindolilo.

En un aspecto de la invención, heteroarilo de C₅ es un grupo cíclico aromático de 5 miembros que contiene 5 átomos en el anillo, 1, 2, ó 3 de los cuales son heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre y los átomos en el anillo restantes son carbono, 15 por ejemplo oxazol.

Como se utiliza aquí, el término "sustituido" se refiere a la sustitución con el sustituyente o sustituyentes nombrados, permitiéndose múltiples grados de sustitución a menos que se manifieste lo contrario.

Para evitar duda, el término "independientemente" significa que 20 cuando se selecciona más de un sustituyente a partir de un número de sustituyentes posibles, aquellos sustituyentes pueden ser iguales o diferentes.

Como se utiliza aquí, el término "farmacéuticamente aceptable" significa un compuesto que es adecuado para uso farmacéutico.

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Sales de compuestos de fórmula (I) que son adecuados para uso en medicina son aquellos en los que el ión es farmacéuticamente aceptable. No obstante, las sales que tienen contraiones no farmacéuticamente aceptables están dentro del alcance de la presente invención, por ejemplo para uso como intermediarios en la preparación de compuestos de fórmula (I) y sus sales farmacéuticamente aceptables.

Sales farmacéuticamente aceptables adecuadas serán evidentes para los expertos en la técnica e incluyen por ejemplo sales ácidas de adición formadas con ácidos inorgánicos, por ejemplo ácido clorhídrico, bromhídrico, sulfúrico, ácido nítrico o fosfórico, y ácidos orgánicos por ejemplo ácido succínico, maleico, málico, mandélico, acético, fumárico, glutámico, láctico, cítrico, tartárico, benzoico, bencensulfónico, *p*-toluensulfónico, metansulfónico, etansulfónico o naftalensulfónico. Otras sales farmacéuticamente no aceptables, por ejemplo oxalatos, pueden usarse por ejemplo en el aislamiento de compuestos de fórmula (I) y se incluyen dentro del alcance de esta invención. Se hace referencia a Berge et al. J. Pharm. Sci., 1977, 66, 1-19.

Ciertos compuestos de fórmula (I) pueden formar sales ácidas de adición con uno o más equivalentes del ácido. La presente invención incluye dentro de su alcance todas las formas estequiométricas y no estequiométricas de las mismas.

Los solvatos de los compuestos de fórmula (I) y solvatos de las sales de los compuestos de fórmula (I) están incluidos dentro del alcance de

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la presente invención.

Como se utiliza en la presente, el término "solvato" se refiere a un complejo de estequiometría variable formada por un soluto (en esta invención un compuesto de fórmula (I) o una sal del mismo) y un solvente.

- 5 Tales solventes para el propósito de la invención pueden no interferir con la actividad biológica del soluto. Ejemplos de solventes adecuados incluyen, pero no se limitan a, agua, metanol, etanol y ácido acético. En un aspecto de la invención, el solvente usado es un solvente farmacéuticamente aceptable. En otro aspecto de la invención, el solvente usado es agua y el solvato
- 10 también puede ser denominado un hidrato.

- Solvatos de compuestos de fórmula (I) que son adecuados para uso en medicina son aquellos en los que el solvente es farmacéuticamente aceptable. No obstante, los solvatos que tienen solventes farmacéuticamente no aceptables están dentro del alcance de la presente invención, por ejemplo
- 15 para uso como intermediarios en la preparación de otros compuestos de fórmula (I) y sus sales farmacéuticamente aceptables.

Profármacos de los compuestos de fórmula (I) se incluyen dentro del alcance de la presente invención.

- Como se utiliza aquí, el término "profármaco" significa un
- 20 compuesto que se convierte dentro del cuerpo, por ejemplo mediante hidrólisis en la sangre, en su forma activa que tiene efectos médicos. Profármacos farmacéuticamente aceptables se describen en T. Higuchi y V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series,

y en Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987 y en D. Fleishner, S. Ramon and H. Barba "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", *Advanced Drug Delivery Reviews* (1996) 19(2) 115-130. Los profármacos son cualesquier portadores enlazados de forma covalente que liberan un compuesto de estructura (I) *in vivo* cuando tal profármaco se administra a un paciente. Los profármacos generalmente se preparan al modificar grupos funcionales de manera que la modificación se escinde *in vivo*, resultando el compuesto de partida. Los profármacos pueden incluir, por ejemplo, compuestos de esta invención en donde los grupos hidroxilo o amina se unen a cualquier grupo que, cuando se administra a un paciente, se escinde para formar los grupos hidroxilo o amina. Así, ejemplos representativos de profármacos incluyen (sin restricción) derivados de fosfonato, carbamato, acetato, formiato y benzoato de grupos funcionales hidroxilo y amina de los compuestos de fórmula (I).

Los fosfonatos, acetatos, benzoatos y carbamatos pueden estar activos por derecho propio y/ o ser hidrolizables bajo condiciones *in vivo* en el cuerpo humano. Grupos de éster hidrolizables farmacéuticamente adecuados *in vivo* incluyen aquellos que se descomponen fácilmente en el cuerpo humano para dejar el ácido de partida o su sal. Un fosfonato se forma mediante reacción con ácido fosforoso (fosfónico), mediante métodos bien conocidos en la técnica. Por ejemplo, los fosfonatos pueden ser derivados como $RP(O)(OR)_2$ y similares. Un acetato es un éster de ácido acético. Un

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benzoato es un éster de ácido bencencarboxílico. Un carbamato es un éster de ácido carbámico.

En un aspecto de la invención se proporciona un compuesto, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto se
5 selecciona del grupo que consiste en:

N-[3,4-bis(Metiloxi)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

N-[3,4-bis(Metiloxi)fenil]-1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

10 1-[(4-Bromofenil)metil]-5-metil-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida,

1-[(4-Fluorofenil)metil]-5-metil-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida,

15 1-[(4-Fluorofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida,

1-[(4-Bromofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida,

5-Metil-1-(fenilmetil)-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida,

20 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida,

1-[(2'-Cloro-4-bifenilil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida,

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5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-[(4-metilfenil)metil]-1H-
1,2,3-triazol-4-carboxamida,

5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-[[4-(1-metiletil)fenil]metil]-
1H-1,2,3-triazol-4-carboxamida,

5 N-[3,4-Bis(metiloxi)fenil]-5-metil-1-[(4-metilfenil)metil]-1H-1,2,3-
triazol-4-carboxamida,

1-(2-Bifenililmetil)-N-[3,4-bis(metiloxi)fenil]-5-metil-1H-1,2,3-
triazol-4-carboxamida,

N-[3,4-Bis(metiloxi)fenil]-1-[(4-fluorofenil)metil]-1H-1,2,3-triazol-4-
10 carboxamida,

1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1,3-oxazol-2-il)fenil]-1H-
1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-
1,2,3-triazol-4-carboxamida,

15 Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
il)carbonil)amino]-3-(metiloxi)benzoato,

1-[(3,4-Diclorofenil)metil]-5-metil-N-{3-[(metilamino)carbonil]fenil}-
1H-1,2,3-triazol-4-carboxamida,

20 1-[(3,4-Diclorofenil)metil]-5-metil-N-{4-[(metilamino)carbonil]fenil}-
1H-1,2,3-triazol-4-carboxamida,

Etil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
il)carbonil)amino]benzoato,

N-[3-(acetilamino)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-

1,2,3-triazol-4-carboxamida,

N-[4-(acetilamino)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-

1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-

5 1H-1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-

1,2,3-triazol-4-carboxamida,

Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)carbonil)amino]-4-(metiloxi)benzoato,

10 1-[(3,4-Diclorofenil)metil]-N-[4-hidroxi-3-(hidroximetil)fenil]-5-

metil-1H-1,2,3-triazol-4-carboxamida,

Etil {4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)carbonil)amino]fenil}acetato,

Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

15 il)carbonil)amino]-2-(metiloxi)benzoato,

Metil 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)carbonil)amino]-2-hidroxibenzoato,

Metil {3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)carbonil)amino]fenil}acetato,

20 1-[(3,4-Diclorofeni)metil]-N-(3-hidroxifenil)-5-metil-1H-1,2,3-

triazol-4-carboxamida,

Metil 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)carbonil)amino]-2-fluorobenzoato,

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N-[5-(Aminocarbonil)-2-(metiloxo)fenil]-1-[(3,4-diclorofenil)metil]-
5-metil-1H-1,2,3-triazol-4-carboxamida,

Metil 4-cloro-3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-
triazol-4-il)carbonil)amino]benzoato,

5 Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
il)carbonil)amino]-4-(metiloxo)fenil]acetato,

Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
il)carbonil)amino]-4-fluorobenzoato,

10 N-[3-(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-
carboxamida, N-[4-(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-
carboxamida,

N-[3-(hidroximetil)-2-metilfenil]-5-metil-1-(fenilmetil)-1H-1,2,3-
triazol-4-carboxamida,

15 1-[(3,5-Diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-
1,2,3-triazol-4-carboxamida,

Metil 3-[(1-[(3,5-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
il)carbonil)amino]-4-(metiloxi)benzoato,

1-[(3,5-Diclorofenil)metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-
1H-1,2,3-triazol-4-carboxamida,

20 N-[3-[(Acetilamino)metil]fenil]-1-[(3,4-diclorofenil)metil]-5-metil-
1H-1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[3-(1-hidroxietil)fenil]-5-metil-1H-
1,2,3-triazol-4-carboxamida,

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N-[4-cloro-3-(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

Dimetil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,2-bencendicarboxilato,

5 Metil 5-[(1-[(3,5-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-2-fluorobenzoato,

Etil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoato,

10 1-[(3,4-Diclorofenil)metil]-N-[4-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[4-(2-hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[5-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

15 N-[3,5-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

20 1-[(3,4-Diclorofenil)metil]-N-[5-(2-hidroxietil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[2-fluoro-5-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,

N-[2-cloro-5-(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-

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1H-1,2,3-triazol-4-carboxamida,

1-[(3,5-Diclorofenil)metil]-N-[5-(hidroximetil)-2-(metiloxi)fenil]-5-

metil-1H-1,2,3-triazol-4-carboxamida,

N-[3,4-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-

5 1,2,3-triazol-4-carboxamida,

1-[(3,5-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-

1H-1,2,3-triazol-4-carboxamida,

N-[3,5-bis(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-

4-carboxamida,

10 N-[3,5-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-

1,2,3-triazol-4-carboxamida,

1-[(3,4-Diclorofenil)metil]-N-[3-(2-hidroxietil)fenil]-5-metil-1H-

1,2,3-triazol-4-carboxamida,

Ácido 3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

15 il)carbonil)amino]benzoico,

Ácido 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)carbonil)amino]-4-(metiloxi)benzoico,

ácido 5-([5-Metil-1-(fenilmetil)-1H-1,2,3-triazol-4-

il)carbonil)amino)-1,3-bencendicarboxílico,

20 Ácido 4-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)carbonil)amino]benzoico,

1-[(3,4-Diclorofenil)metil]-N-{3-[(etilamino)carbonil]fenil}-5-metil-

1H-1,2,3-triazol-4-carboxamida,

- 1-[(3,4-Diclorofenil)metil]-N-(3-[(2-hidroxi)etil]amino)carbonil}fenil)-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 1-[(3,4-Diclorofenil)metil]-5-metil-N-[5-[(metilamino)carbonil]-2-(metiloxi)fenil]-1H-1,2,3-triazol-4-carboxamida,
- 5 {3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil]amino}fenil}metil acetato,
- {3-[(1-[(3,5-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil]amino}fenil}metil acetato,
- {3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil]amino}fenil}metil benzoato,
- 10 {3-[(1-[(3,5-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil]amino}fenil}metil benzoato,
- 1-[(3,4-Diclorofenil)metil]-N-{4-[(2-hidroxi)etil]oxi}fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 15 1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1-metiletenil)-2-(metiloxi)fenil]-1H-1,2,3-triazol-4-carboxamida,
- 1-[(3,4-Diclorofenil)metil]-N-[3-(1-hidroxi-1-metiletil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 1-[(3,4-Diclorofenil)metil]-N-[4-{2-(dimetilamino)etil}oxi]-3-
- 20 (hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 1-[(3,4-Diclorofenil)metil]-N-{3-[(2-hidroxi)etil]oxi}fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida, o
- {5-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-

il)metil)amino]benceno-1,3-diil}dimetanol.

En otro aspecto de la invención se proporciona un compuesto, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto se selecciona del grupo que consiste en:

- 5 N-[3,4-bis(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida,
- N-[3,5-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- N-[3,4-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 10 N-[3,4-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- N-[3,5-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 15 N-[3,4-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 1-[(3-clorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 1-[(4-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 20 1-[(3-clorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida,
- 1-[(3-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-

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triazol-4-carboxamida,

1-[(4-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-

triazol-4-carboxamida,

1-[(3-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-

5 triazol-4-carboxamida

1-[(3,4-diclorofenil)metil]-N-{3-(hidroximetil)-5-

[(metilamino)carbonil]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida, o

N-{1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}-4-

(hidroximetil)benzamida.

- 10 Se ha encontrado que los compuestos de la invención inhiben la actividad de SCD y por ello pueden ser útiles para regular los niveles de lípidos, por ejemplo niveles de lípido en plasma. Las enfermedades o condiciones ocasionadas por o asociadas con un perfil anormal de lípidos en plasma y para el tratamiento del cual los compuestos de la invención pueden
- 15 ser útiles incluyen: dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, apoplejía, infarto al miocardio, aterosclerosis, obesidad, diabetes tipo I, diabetes tipo II, resistencia a insulina, hiperinsulinemia y síndrome metabólico. Otras
- 20 enfermedades cardiovasculares para los cuales son útiles los compuestos de la presente invención incluyen enfermedad vascular periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de diabetes y trombosis. Otras enfermedades o condiciones incluyen

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esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras enfermedades relacionadas con acumulaciones de lípidos en el hígado.

Los compuestos de la invención también pueden ser útiles en el tratamiento de trastornos de la piel por ejemplo eczema, acné, psoriasis, 5 envejecimiento de la piel, formación o prevención de cicatrices queloides y enfermedades relacionadas con la producción o secreciones de membranas mucosas.

Los compuestos de la invención también pueden ser útiles en el tratamiento de cáncer, neoplasia, tumor maligno, metástasis, tumores 10 (benignos o malignos), carcinogénesis, hepatomas y similares.

Los compuestos de la invención también pueden ser útiles en el tratamiento de deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloide cerebral (CAA) o demencia asociada con el síndrome de Down (DS) y otras enfermedades neurodegenerativas caracterizadas por la 15 formación o acumulación de placas amiloides que comprenden A β 42.

Dentro del contexto de la presente invención, los términos que describen las indicaciones usadas aquí se clasifican en el Merck Manual of Diagnosis and Therapy, 17^{va} edición y/o en la International Classification of Diseases 10^a edición (ICD-10). Los diversos subtipos de los trastornos 20 mencionados aquí se contemplan como parte de la presente invención.

En un aspecto, la invención proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para uso en terapia médica.

En un aspecto, la invención proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para la fabricación de un medicamento para tratar y/o prevenir una enfermedad o una condición susceptible de mejora mediante un inhibidor de SCD.

5 En otro aspecto, la invención proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para la fabricación de un medicamento para tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, cáncer, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes tipo II, resistencia a insulina,
10 hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no alcohólica (NASH).

En otro aspecto, la invención proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para la fabricación de un medicamento para tratar y/o prevenir acné, psoriasis,
15 envejecimiento de la piel, cáncer, dislipidemia, aterosclerosis, resistencia a insulina, hiperinsulinemia, diabetes tipo II y/o esteatosis hepática.

En otro aspecto, la invención proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para la fabricación de un medicamento para tratar y/o prevenir acné.

20 En un aspecto, la invención proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para su uso para tratar y/o prevenir una enfermedad o una condición susceptible de mejora mediante un inhibidor de SCD en un mamífero, incluyendo un

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humano.

En otro aspecto, la invención proporciona el uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para su uso en tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, 5 cáncer, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes tipo II, resistencia a insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no alcohólica (NASH).

En otro aspecto, la invención proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para su uso en 10 tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, cáncer, dislipidemia, aterosclerosis, resistencia a insulina, hiperinsulinemia, diabetes tipo II y/o esteatosis hepática.

En otro aspecto, la invención proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para uso en el 15 tratamiento y/o prevención de acné.

En un aspecto, la invención proporciona un método para tratar y/o prevenir una enfermedad o una condición susceptible a mejora mediante un inhibidor de SCD, cuyo método comprende administrar a un sujeto, por ejemplo a un mamífero, incluyendo un humano, una cantidad 20 terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la invención proporciona un método para tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, cáncer, dislipidemia,

hipertrigliceridemia, aterosclerosis, obesidad, diabetes tipo II, resistencia a insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no alcohólica (NASH), cuyo método comprende administrar a un sujeto, por ejemplo a un mamífero, incluyendo un humano, una cantidad
5 terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la invención proporciona un método para tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, cáncer, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes tipo II, resistencia a
10 insulina, hiperinsulinemia y/o esteatosis hepática, cuyo método comprende administrar a un sujeto, por ejemplo a un mamífero, incluyendo un humano, una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la invención proporciona un método para tratar
15 y/o prevenir acné, cuyo método comprende administrar a un sujeto, por ejemplo a un mamífero, incluyendo un humano, una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

Se observará que la referencia a "tratamiento" y "terapia" incluye
20 el tratamiento agudo de profilaxis así como el alivio de síntomas establecidos.

Ya que los compuestos de la invención tienen como propósito su uso en composiciones farmacéuticas se entenderá fácilmente que se proporcionan cada uno en forma sustancialmente pura, por ejemplo al menos

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60% de pureza, más adecuadamente al menos 75% de pureza y preferiblemente al menos 85%, en especial al menos 98% de pureza (los porcentajes son peso por peso). Las preparaciones impuras de los compuestos pueden usarse para preparar las formas más puras usadas en las composiciones farmacéuticas; estas preparaciones menos puras de los compuestos deben contener al menos 1%, más adecuadamente al menos 5% y preferiblemente de 10% a 59% de un compuesto de la invención.

Procedimientos para la preparación de los compuestos de fórmula (I) forman aspectos adicionales de la invención. R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 y X son como se define a menos que se especifique lo contrario. A lo largo de la descripción, las fórmulas generales se designan mediante números romanos (I), (II), (III), (IV) etc.

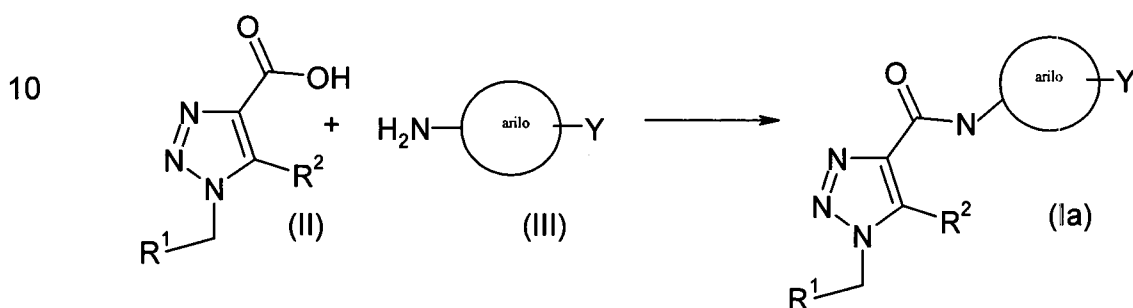
En ciertos casos los compuestos finales de fórmula (I) pueden convertirse a otros compuestos de fórmula (I) mediante técnicas conocidas por los expertos en la técnica, por ejemplo, los sustituyentes de ácido carboxílico pueden convertirse a ésteres o amidas mediante técnicas rutinarias.

En un procedimiento general, los compuestos de fórmula (I), en donde X representa -CONH- y R^3 representa, , en donde  representa arilo de C_{6-10} e Y representa alquilo de C_{1-6} , alcoxi de C_{1-6} , alquilo $O(CH_2)_mR^4$, $-C_{0-6}OH$, $-(CH_2)_nCO_2R^5$, $-(C=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, haloalquilo de C_{1-6} , haloalquilo de OC_{1-6} , cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} , halógeno o heteroarilo de C_5 ,

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(fórmula (Ia)), pueden prepararse de acuerdo con el esquema de reacción 1 al hacer reaccionar los compuestos de fórmula (II) y los compuestos de fórmula (III). La reacción se lleva adecuadamente a cabo en presencia de un reactivo de acoplamiento como HATU o EDCI y HOBT y una base como DIPEA o NEt_3 en un solvente adecuado como DMF (de forma adecuada de temperatura ambiente a 40°C).

Esquema de reaccion 1



En consecuencia, en un aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (Ia) al hacer reaccionar un compuesto de fórmula (II), en donde R^1 y R^2 se definen arriba, con un compuesto de fórmula (III) en donde Y y  se definen arriba, en presencia de un agente de acoplamiento.

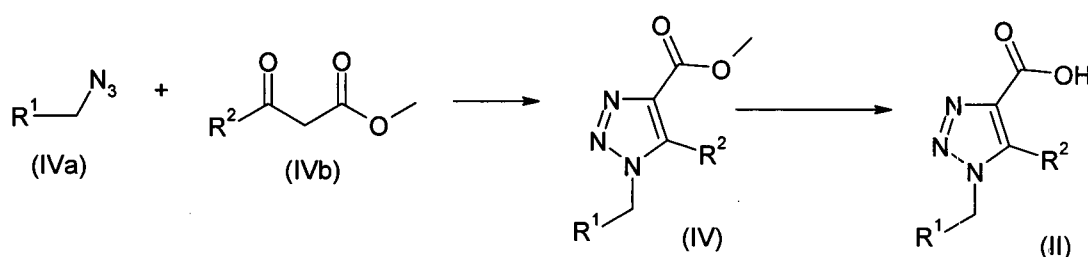
Los compuestos de fórmula (II) pueden prepararse de acuerdo con el esquema de reacción 2 al hacer reaccionar compuestos de fórmula (IVa) y compuestos de fórmula (IVb). La reacción se lleva a cabo adecuadamente en presencia de una base como carbonato de potasio en un solvente adecuado como DMF o DMSO (de forma adecuada a $40-80^\circ\text{C}$), a lo

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que le sigue la saponificación de los compuestos de fórmula (IV) en condiciones básicas como hidróxido de sodio en un solvente adecuado, como etanol o metanol (para someter a reflujo).

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Esquema de reaccion 2

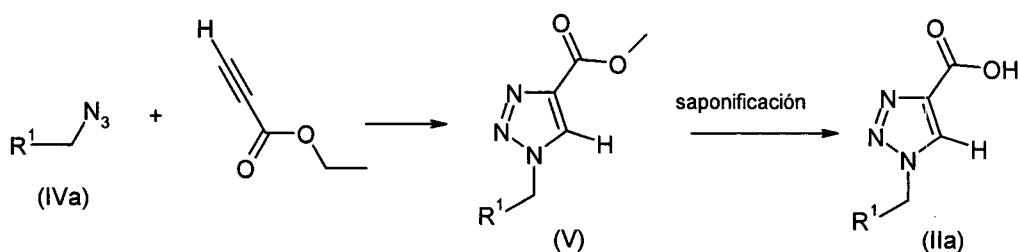


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Los compuestos de fórmula (II), en donde R^2 representa H (fórmula (IIa)), pueden prepararse de acuerdo con el esquema de reacción 3 al hacer reaccionar compuestos de fórmula (IVa) y etil 2-propinoato en un solvente adecuado como etanol a reflujo, a lo que le sigue la saponificación de los compuestos de fórmula (V) en condiciones básicas como hidróxido de sodio en un solvente adecuado, como etanol o metanol (de forma adecuada a reflujo).

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esquema de reaccion 3

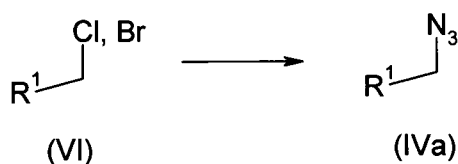


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Los compuestos de fórmula (IVa) pueden prepararse de acuerdo con el esquema de reacción 4 mediante la reacción de bencil haluro de cloro o bromo (VI) con azida de sodio en un solvente adecuado como DMSO o DMF (de forma adecuada a temperatura ambiente a 80°C).

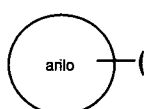
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Esquema de reaccion 4



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Los compuestos de fórmula (I), en donde R³ representa



(Alquilo de C₁₋₆)

y

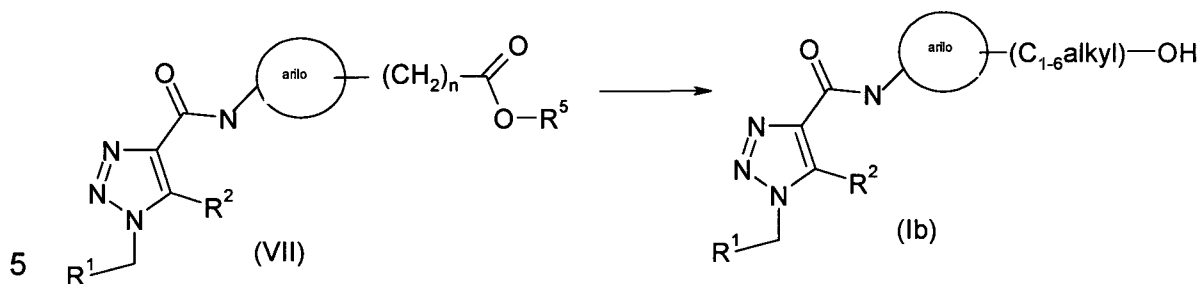


se define arriba (fórmula (Ib)),

también pueden prepararse de acuerdo con el esquema de reacción 5 mediante reducción de la función éster (Y = -(CH₂)_nCOOR⁵) de los compuestos de fórmula (VII) en presencia de DIBAL-H en una solución de tolueno. La reacción se lleva a cabo adecuadamente en un solvente adecuado como THF a temperatura ambiente.

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esquema de reaccion 5



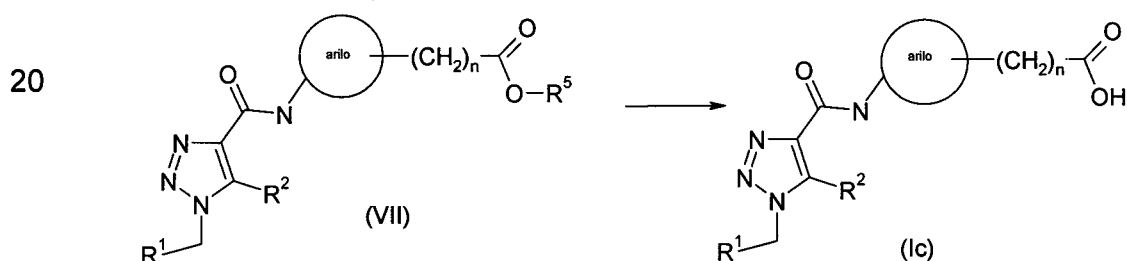
En consecuencia, en otro aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (Ib) mediante reducción de la función éster ($\text{Y} = \text{---}(\text{CH}_2)_n\text{COOR}^5$) de los compuestos de fórmula (VII), en donde R^1 , R^2 y  se definen arriba.

10

Los compuestos de fórmula (I), en donde R^3 representa  $\text{---}(\text{CH}_2)_n\text{---COOH}$ y  se define arriba (fórmula (Ic)), también pueden prepararse de acuerdo con el esquema de reacción 6 mediante reducción de la función éster ($\text{Y} = \text{---}(\text{CH}_2)_n\text{COOR}^5$) de los compuestos de fórmula (VII) en condiciones básicas en un solvente adecuado como metanol o etanol, de forma adecuada a reflujo.

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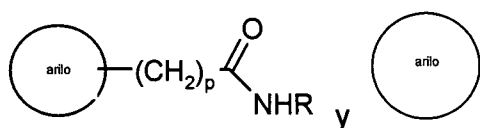
Esquema de reaccion 6



En consecuencia, en otro aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (Ic) mediante saponificación de la función éster ($Y = -(\text{CH}_2)_n\text{COOR}^5$) de compuestos de fórmula (VII), en donde R^1 , R^2 y  se definen arriba en condiciones

5 básicas.

Los compuestos de fórmula (I), en donde R^3 representa

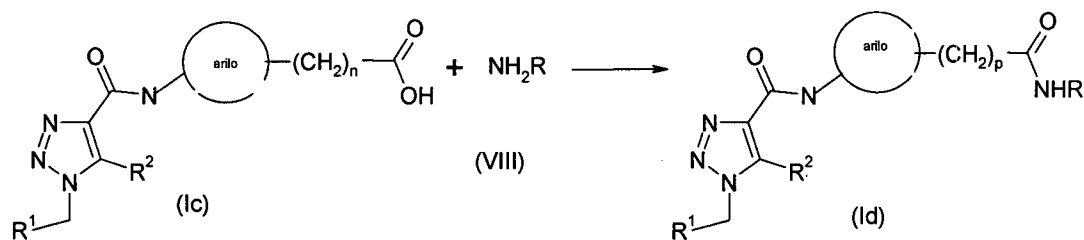


se define arriba la fórmula (Id)), pueden prepararse de acuerdo con el esquema de reacción 7 al hacer reaccionar los compuestos de fórmula (Ic) y los compuestos de fórmula (VIII), en donde R

10 representa R^6 o R^7 , en presencia de un reactivo de acoplamiento como HATU, HOBT o EDCI y una base como DIPEA o NEt_3 en un solvente adecuado como DMF (de forma adecuada de temperatura ambiente a 40°C).

Esquema de reaccion 7

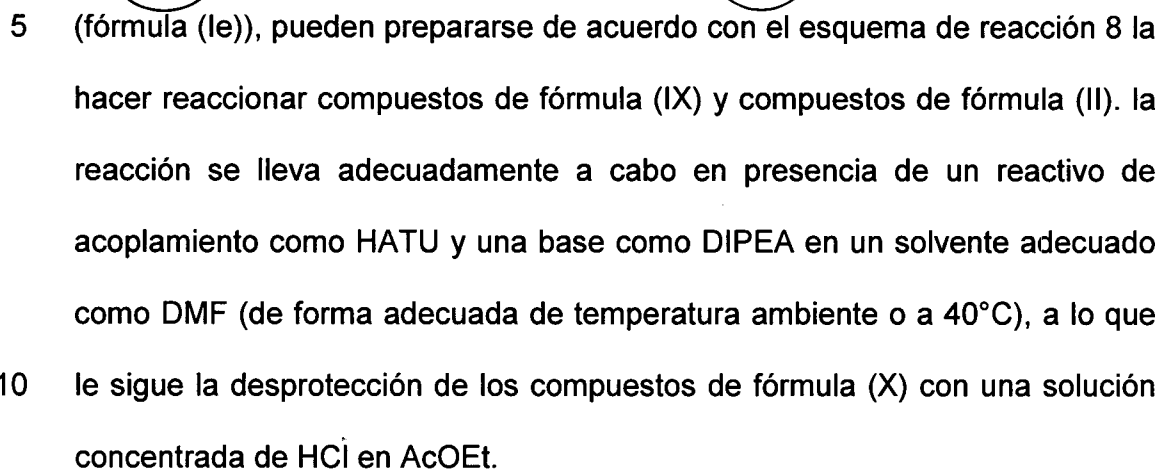
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En consecuencia, en otro aspecto la invención proporciona un

20 procedimiento para la preparación de compuestos de fórmula (Id) al hacer reaccionar compuestos de fórmula (Ic), en donde R^1 , R^2 y  se

Los compuestos de fórmula (I), en donde R^3 representa



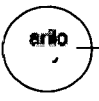
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En consecuencia, en otro aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (Ie) al hacer reaccionar compuestos de fórmula (II), en donde R¹ y R² se definen arriba, con

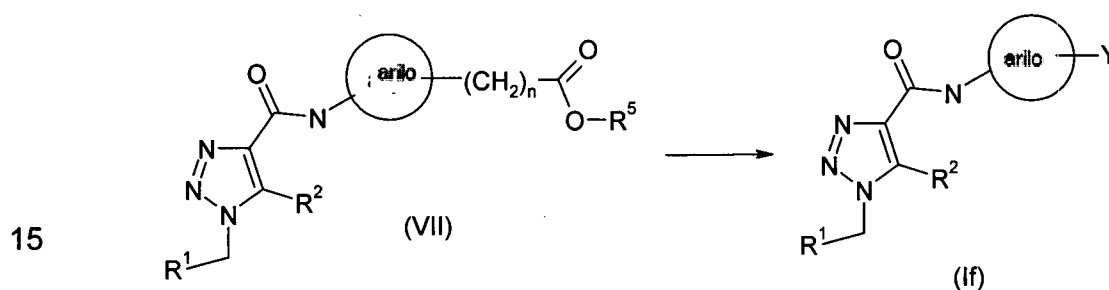
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compuestos de fórmula (IX) en donde  se define arriba, en presencia de un agente de acoplamiento, seguido por desprotección de compuestos de fórmula (X).

5  Los compuestos de fórmula (I), en donde R^3 representa -Y se define arriba e Y representa alquilo $C_{0-6}OH$ (como -C(CH₃)₃OH) (fórmula (If)), pueden prepararse de acuerdo con el esquema de reacción 9 al hacer reaccionar los compuestos de fórmula (VII) en presencia de una solución de bromuro de metil magnesio en THF (de forma adecuada a temperatura ambiente o a 60°C).

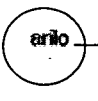
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Esquema de reaccion 9



En consecuencia, en otro aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (If) en donde  e Y se definen arriba al hacer reaccionar compuestos de fórmula (VII), en donde R^1 y R^2 se definen arriba, en presencia de un bromuro de metil magnesio.

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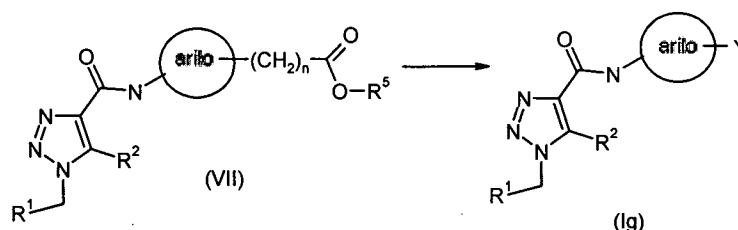
Los compuestos de fórmula (I), en donde R^3 representa -Y  se define arriba e Y representa alquenilo C_{1-6} (fórmula

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(Ig)), pueden prepararse de acuerdo con el esquema de reacción 10 al hacer reaccionar los compuestos de fórmula (VII) en presencia de una solución de bromuro de metil magnesio en THF (de forma adecuada a temperatura ambiente o a 60°C).

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Esquema de reaccion 10



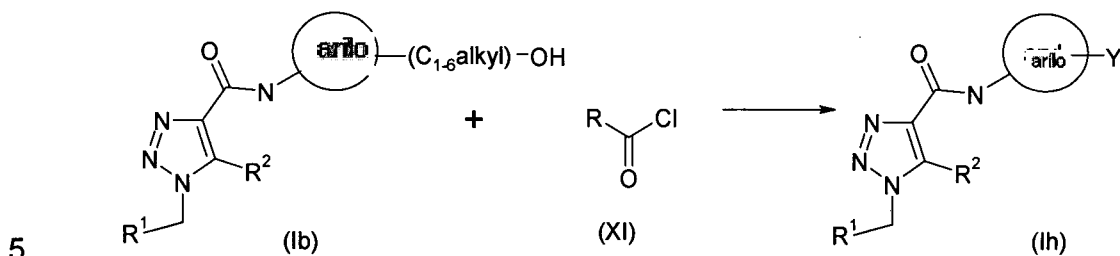
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En consecuencia, en otro aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (Ig) en donde  e Y se definen arriba al hacer reaccionar compuestos de fórmula (VII), en donde R¹ y R² se definen arriba, en presencia de un bromuro de metil magnesio.

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Compuestops de fórmula (I), en donde R³ representa ,  se define arriba e Y representa $-(CH_2)_mOC(=O)R^4$ o $-(CH_2)_nOC(=O)R^5$ (fórmula (Ih)), pueden prepararse de acuerdo con el esquema de reacción 11 mediante la reacción de compuestos de fórmula (Ib) con compuestos de fórmula (XI), en donde R representa R⁴ o R⁵, en solvente adecuado como una mezcla de DCM y THF (de forma adecuada a temperatura ambiente adecuada).

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Esquema de reaccion 11

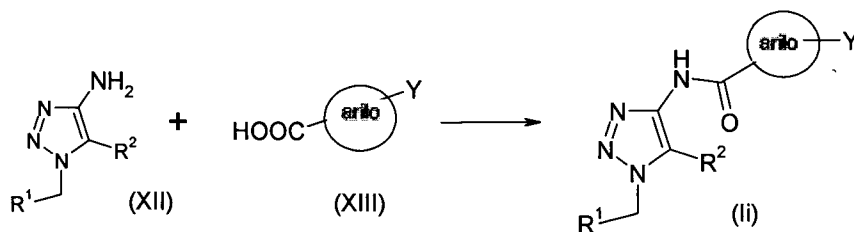
En consecuencia, en otro aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (Ih) en donde  e Y se definen arriba al hacer reaccionar compuestos de fórmula (Ib), en donde R¹ y R² se definen arriba, con compuestos de fórmula (XI), en donde R se define arriba.

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Los compuestos de fórmula (I), en donde X representa -NHCO- y R³ representa -Y, en donde  e Y se definen como arriba ((fórmula (Ii), pueden prepararse de acuerdo con el esquema de reacción 12 al hacer reaccionar compuestos de fórmula (XII) y compuestos de fórmula (XIII). La reacción se lleva adecuadamente a cabo en presencia de un reactivo de acoplamiento como HATU y una base como DIPEA en un solvente adecuado como DCM o DMF (de forma adecuada de temperatura ambiente a 40°C).

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Esquema de reaccion 12

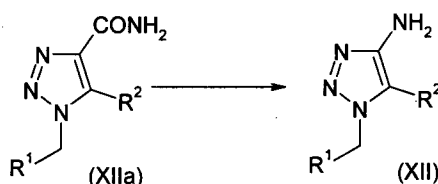
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En consecuencia, en otro aspecto la invención proporciona un procedimiento para la preparación de compuestos de fórmula (li) al hacer reaccionar compuestos de fórmula (lc), en donde R^1 y R^2 y R^3 representa

de fórmula (XIII) en donde aryl e Y se definen arriba, en presencia de un reactivo de acoplamiento.

Los compuestos de fórmula (XII), en donde R^1 y R^2 , se definen arriba pueden prepararse de acuerdo con el esquema de reacción 13 al hacer reaccionar los compuestos de fórmula (XIIa) en presencia de bromo y una base como hidróxido de potasio en un solvente adecuado como agua (de forma adecuada de 40° a 80°C).

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Esquema de reaccion 13

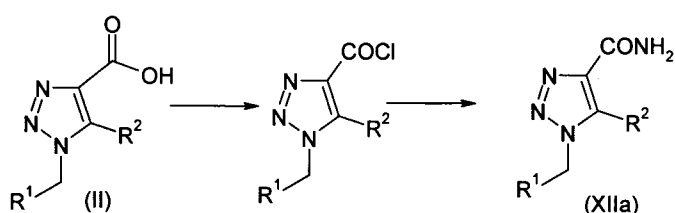
Los compuestos de fórmula (XIIa), en donde R^1 y R^2 , se definen arriba pueden prepararse de acuerdo con el esquema de reacción 14 al hacer

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reaccionar los compuestos de fórmula (II) en presencia de cloruro de tionilo en cloroformo a temperatura ambiente, seguido por una reacción con amoníaco acuoso en acetonitrilo en hielo (por ejemplo -5 a 5°C).

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Esquema de reacción 14



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Los compuestos de fórmula (III) (IVb), (VI), (VIII), (IX), (XI) y (XIII) son compuestos comercialmente disponibles o pueden prepararse mediante métodos conocidos en la literatura o procedimientos conocidos por los expertos en la técnica. Los compuestos de fórmula (VIII) pueden prepararse conforme al esquema general de reacción 1.

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Detalles adicionales para la preparación de compuestos de fórmula (I) se encuentran en la sección de ejemplos en lo sucesivo.

Los compuestos de la invención pueden prepararse individualmente o como bibliotecas de compuestos que comprenden al menos 2, por ejemplo 5 a 1,000 compuestos, y más preferiblemente 10 a 100 compuestos. Las bibliotecas de compuestos de la invención pueden prepararse mediante un enfoque de combinación "divida y mezcle" o mediante múltiples síntesis paralelas usando la química en fase de solución o en fase sólida, mediante procedimientos conocidos por los expertos en la técnica. Así,

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de conformidad con un aspecto adicional se proporciona una biblioteca de compuestos que comprende al menos 2 compuestos de la invención.

Los expertos en la técnica observarán que en la preparación de los compuestos de fórmula (I) y/o solvatos de los mismos puede ser necesario y/o deseable proteger uno o más grupos sensibles en la molécula o en el intermediario apropiado para prevenir reacciones secundarias indeseadas. Grupos protectores adecuados para uso de acuerdo con la presente invención son bien conocidos por los expertos en la técnica y pueden usarse de manera convencional. Ver por ejemplo "Protective groups in organic synthesis" por T.W. Greene y P.G.M. Wuts (John Wiley & sons 1991) o "Protecting Groups" por P.J. Kocienski (Georg Thieme Verlag 1994). Ejemplos de grupos protectores de amino adecuados incluyen grupos protectores tipo acilo (por ejemplo formilo, trifluoroacetilo, acetilo), grupos protectores tipo uretano aromáticos (por ejemplo . benciloxycarbonilo (Cbz) y Cbz sustituido), grupos protectores de uretano alifáticos (por ejemplo 9-fluorenilmetoxycarbonilo (Fmoc), t-butiloxycarbonilo (Boc), isopropiloxycarbonilo, ciclohexiloxycarbonilo) y grupos protectores tipo alquilo o aralquilo (por ejemplo bencilo, tritilo, clorotritilo).

Varios compuestos intermedios usados en los procedimientos mencionados arriba, incluyendo sin restricción ciertos compuestos de fórmulas (IV), (V) y (X), constituyen un aspecto adicional de la presente invención.

Los compuestos de fórmula (I) o sal(es) farmacéuticamente aceptable(s) de los mismos también pueden usarse en combinación con otros

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agentes terapéuticos. Así, la invención proporciona en un aspecto adicional una combinación que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo junto con uno o más agentes terapéuticos.

- 5 Los compuestos de la invención pueden administrarse en combinación con otros agentes terapéuticos. Agentes terapéuticos preferidos se seleccionan de la lista: un inhibidor de colesterol éster transferasa (inhibidores de CETP), un inhibidor de HMG-CoA reductasa, una proteína de transferencia de triglicéridos microsomal, un activador del receptor de peroxisoma activado por proliferador (PPAR), un inhibidor de la recaptación de ácido de bilis, un inhibidor de absorción de colesterol, un inhibidor de la síntesis de colesterol, un fibrato, niacina, una resina de intercambio de iones, un antioxidante, un inhibidor de AcylCoA: colesterol aciltransferasa (inhibidor de ACAT), un antagonista de cannabinoide 1, un secuestrador de ácido de bilis. Otros agentes terapéuticos preferidos se seleccionan de la lista: un corticosteroide, un derivado de vitamina D3, un retinoide, un inmunomodulador, un antiandrógeno, un agente queratolítico, un antimicrobiano, un quimioterapéutico de platino, un antimetabolito, hidroxiurea, un taxano, un interruptor mitótico, una antraciclina, dactinomicina, un agente de alquilación y un inhibidor de colinesterasa.
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- 15
- 20

Cuando el compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo se usa en combinación con un segundo agente terapéutico la dosis de cada compuesto puede diferir de

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aquella en la que el compuesto es usado solo. Los expertos en la técnica apreciarán las dosis apropiadas. Se observará que la cantidad de un compuesto de la invención requerido para uso en tratamiento variará con la naturaleza de la condición que se esté tratando y la edad y condición del

5 paciente y al final a discreción del médico o veterinario tratante.

Las combinaciones mencionadas arriba pueden presentarse convenientemente para su uso en forma de una formulación farmacéutica y por ende las formulaciones farmacéuticas que comprenden una combinación como se define arriba junto con al menos un portador y/o excipiente

10 farmacéuticamente aceptable comprenden un aspecto adicional de la invención. Los componentes individuales de tales combinaciones pueden administrarse ya sea en secuencia o simultáneamente en formulaciones farmacéuticas separadas o combinadas mediante cualquier ruta conveniente.

Cuando la administración es en secuencia, ya sea el inhibidor de

15 SCD o el segundo agente terapéutico pueden administrarse primero. Cuando la administración es simultánea, la combinación puede administrarse ya sea en la misma o en diferente composición farmacéutica.

Cuando se combinan en la misma formulación se observará que los dos compuestos deben ser estables y compatibles uno con el otro y con

20 los otros componentes de la formulación. Cuando se formulan por separado pueden proveerse en cualquier formulación conveniente, de manera tal que sean conocidos para tales compuestos en la técnica.

La invención también incluye una composición farmacéutica que

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comprende uno o más compuestos de fórmula (I) o sales farmacéuticamente aceptables en combinación con uno o más excipientes.

Los compuestos de la invención pueden administrarse en formas de dosificación convencionales preparadas al combinar un compuesto de la invención con portadores o diluyentes farmacéuticos estándares de acuerdo con procedimientos convencionales bien conocidos en la técnica. estos procedimientos pueden involucrar mezclar, granular y comprimir o disolver los ingredientes como sea apropiado a la preparación deseada.

Las composiciones farmacéuticas de la invención pueden formularse para administración por cualquier ruta, e incluyen aquellas en una forma adaptada para administración, oral, tópica o parenteral a mamíferos incluyendo humanos.

Las composiciones pueden estar en forma de tabletas, cápsulas, polvos, gránulos, pastillas, cremas o preparaciones líquidas, como soluciones o suspensiones orales o parenterales estériles.

Las formulaciones tópicas de la presente invención pueden presentarse como, por ejemplo, ungüentos, cremas o lociones, ungüentos para los ojos y gotas para los ojos u oídos, apósitos impregnados y aerosoles, y pueden contener aditivos convencionales apropiados como conservadores, solventes para ayudar a la penetración del fármaco y emolientes en ungüentos y cremas.

Las cremas, lociones o ungüentos pueden prepararse como productos de aplicación y enjuague o dejarse aplicados en sitio, así como

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productos de tratamiento en dos etapas para uso con otras composiciones de limpieza de la piel o aplicación. Las composiciones pueden administrarse como un producto de aplicación y enjuague en una forma de mayor concentración, como un gel, y luego como un producto que se deja aplicado en sitio en una menor concentración para evitar la irritación de la piel. Cada una de estas formas las entienden bien los expertos en la técnica de manera tal que las dosificaciones pueden prepararse fácilmente para incorporar la composición farmacéutica de la invención.

Los ungüentos son formulaciones semisólidas a base de hidrocarburos que contienen fármacos disueltos o suspendidos. Las cremas y lociones son sistemas de emulsión semisólidos y el término se aplica tanto al agua/aceite o aceite/agua. Las formulaciones en gel son sistemas semisólidos en los cuales una fase líquida está atrapada en una matriz polimérica.

Como ejemplo no restrictivo los ungüentos pueden contener uno o más portadores hidrófobos seleccionados de, por ejemplo, parafina suave blanca u otras ceras minerales, parafina líquida, ceras no minerales, alcoholes de cadena larga, ácidos de cadena larga y siliconas. El ungüento puede contener además de los portadores hidrófobos algunos portadores hidrófilos seleccionados de, por ejemplo, propilenglicol y polietilenglicol en combinación con un sistema tensoactivo/co-tensoactivo apropiado. Las composiciones de portador de las cremas o lociones típicamente son a base de agua, parafina suave blanca y un sistema apropiado de tensoactivo/co-tensoactivo, en combinación con otros portadores/componentes

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seleccionados de, por ejemplo, propilenglicol, butilenglicol, monoestearato de glicerina, PEG-monoestearato de glicerina, ésteres como C₁₂₋₁₅ alquil benzoato, parafina líquida, ceras no minerales, alcoholes de cadena larga, ácidos de cadena larga, siliconas, polímeros que no son de silicona. Los geles
5 pueden formularse por ejemplo mediante el uso de alcohol isopropílico o alcohol etílico, propilenglicol y agua con un agente de gelificación como hidroxietilcelulosa, de forma adecuada en combinación con componentes menores, por ejemplo uno o más de butilenglicol y un agente humectante como un poloxámero.

10 Un ungüento, crema, loción, gel y similares pueden comprender adicionalmente un agente humectante. El agente humectante puede ser un agente humectante hidrófobo como ceramida, aceite de borraja, tocoferol, linoleato de tocoferol, dimeticona o una mezcla de éstos o un agente humectante hidrófilo como glicerina, ácido hialurónico, ácido
15 peroxilínecarbónico y sodio, proteína de trigo, aminoácidos de queratina del cabello o una mezcla de éstos.

Las composiciones de conformidad con la invención pueden comprender también aditivos y adyuvantes convencionales para aplicaciones dermatológicas, como conservadores, ácidos o bases usados como
20 excipientes reguladores de pH y antioxidantes.

La presente invención abarca la administración vía un parche transdérmico u otras formas de administración transdérmica. Formulaciones adecuadas para administración transdérmica se conocen en la técnica y

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pueden emplearse en los métodos de la presente invención. Por ejemplo, formulaciones de parche transdérmico adecuadas para la administración de un compuesto farmacéutico se describen en, por ejemplo, la patente de los Estados Unidos No. 4, 460,372 otorgada a Campbell et al., la patente de los Estados Unidos No. 4,573,996 otorgada a Kwiatek et al., la patente de los Estados Unidos No. 4,624,665 a Nuwayser, la patente de los Estados Unidos No. 4,722,941 a Eckert et al., y la patente de los Estados Unidos No. 5,223,261 a Nelson et al.

Un tipo adecuado de parche transdérmico para uso en los métodos de la presente invención abarca un parche transdérmico adecuado que incluye una capa de respaldo que es no permeable, una capa superficial permeable, una capa adhesiva sustancialmente continua que cubre la capa superficial permeable, y un depósito ubicado o intercalado entre la capa de respaldo y y la capa de superficie permeable de manera que la capa de respaldo se extiende alrededor de los lados del depósito y y se une a la capa de superficie permeable en los bordes de la capa de superficie permeable. El depósito contiene un compuesto de fórmula (I) o sal farmacéuticamente aceptable del mismo, solo o en combinación, y está en contacto fluido con la capa de superficie permeable. El parche transdérmico se adhiere a la piel mediante la capa adhesiva en la capa de superficie permeable, de manera que la capa de superficie permeable está en contacto sustancialmente continuo con con la piel cuando el parche transdérmico se adhiere a la piel. Mientras el parche transdérmico se adhiere a la piel del sujeto, el compuesto

de fórmula (I) o sal farmacéuticamente aceptable del mismo contenido en el depósito del parche transdérmico se transfiere vía la capa de superficie permeable, desde el depósito, a través de la capa adhesiva, y a la piel del paciente. El parche transdérmico también puede incluir opcionalmente uno o
5 más agentes mejoradores de penetración en el depósito que mejoran la penetración del compuesto de fórmula (I) o sal farmacéuticamente aceptable del mismo a través de la piel.

Ejemplos de materiales adecuados que pueden comprender la capa de respaldo se conocen bien la técnica de suministro por parche
10 transdérmico y se puede utilizar cualquier material de capa de respaldo convencional en el parche transdérmico de la invención en cuestión.

Se conocen igualmente en la técnica agentes mejoradores de penetración adecuados. Ejemplos de agentes mejoradores de penetración convencionales incluyen alcanoles como etanol, hexanol, ciclohexanol y
15 similares, hidrocarburos como hexano, ciclohexano, isopropilbenceno; aldehídos y cetonas como ciclohexanona, acetamida, N,N-di(alquil inferior)acetamidas como N,N-dietilacetamida, N,N-dimetil acetamida, N-(2-hidroxietil) acetamida, ésteres como ,N-di-alquil inferior sulfóxidos; aceites esenciales como as propilenglicol, glicerina, monolaurato de glicerol, isopropil
20 miristato y etil oleato, salicilatos, y mezclas de cualquiera de los anteriores.

Tabletas y cápsulas para administración oral pueden estar en forma de presentación de dosis unitaria y pueden contener excipientes convencionales como agentes aglutinantes, por ejemplo jarabe, acacia,

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gelatina, sorbitol, tragacanto o polivinilpirrolidona; llenadores, por ejemplo lactosa, azúcar, almidón de maíz, fosfato de calcio, sorbitol o glicina; lubricantes para formadores de tableta, por ejemplo estearato de magnesio, talco, polietilenglicol o sílice; desintegrantes, por ejemplo almidón de papa; o

5 agentes humectantes adecuados como lauril sulfato de sodio. Las tabletas pueden recubrirse con métodos bien conocidos en la práctica farmacéutica normal. Preparaciones líquidas orales pueden estar en la forma de, por ejemplo, suspensiones acuosas o aceitosas, soluciones, emulsiones, jarabes o elixires, o pueden presentarse como un producto seco para reconstitución

10 con agua u otro vehículo adecuado antes de su uso. Tales preparaciones líquidas pueden contener aditivos convencionales, como agentes de suspensión, por ejemplo sorbitol, metilcelulosa, jarabe de glucosa, gelatina, hidroxietilcelulosa, carboximetilcelulosa, gel de estearato de aluminio o grasa comestibles hidrogenadas, agentes emulsionantes, por ejemplo lecitina,

15 monooleato de sorbitán o acacia; vehículos no acuosos (que pueden incluir aceites comestibles), por ejemplo aceite de almendra, ésteres aceitosos como glicerina, propilenglicol o alcohol etílico; conservadores como por ejemplo metil o propil *p*-hidroxibenzoato o ácido sórbico y, si se desea, agentes saborizantes o colorantes convencionales.

20 Preparaciones para administración oral pueden formularse adecuadamente para dar una liberación controlada/extendida del compuesto activo.

Los supositorios contendrán bases convencionales para

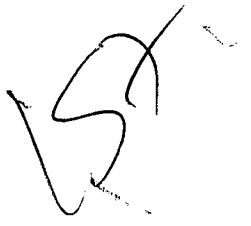
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supositorios, por ejemplo manteca de cacao u otro glicérido.

Para administración parenteral, las formas de dosificación unitarios en fluido se preparan utilizando el compuesto y un vehículo estéril, prefiriéndose agua. El compuesto, dependiendo del vehículo y la
5 concentración usada. puede ya sea suspenderse o disolverse en el vehículo. Al preparar soluciones el compuesto puede disolverse en agua para inyección y esterilizarse por filtro antes de llenarlo en un frasco o ampolla adecuados y sellarlo.

Convenientemente, agentes como un anestésico local,
10 conservador y agentes reguladores pueden disolverse en el vehículo. Para mejorar la estabilidad, la composición puede congelarse después de llenarse en el frasco y el agua retirarse bajo vacío. El polvo liofilizado seco se sella luego en el frasco y se puede suministrar un frasco acompañante de agua para inyección para reconstituir el líquido previo a su uso. Las suspensiones
15 parenterales se preparan sustancialmente de la misma manera excepto que el compuesto se suspende en el vehículo en vez de disolverse y la esterilización no puede lograrse mediante filtración. El compuesto puede esterilizarse mediante exposición a óxido de etileno antes de suspenderlo en el vehículo estéril. Convenientemente, un tensoactivo o agente humectante se incluye en
20 la composición para facilitar la distribución uniforme del compuesto.

La composición puede contener desde 0.1% en peso, preferiblemente desde 10-60% en peso, del ingrediente activo, dependiendo del método de administración. Cuando las composiciones comprenden



unidades de dosificación, cada unidad contendrá preferiblemente de 50-500 mg del ingrediente activo. La dosificación como se emplea para tratamiento en humanos adultos preferiblemente irá en la escala de 100 a 3000 mg por día, por ejemplo 1500 mg por día, dependiendo de la ruta y frecuencia de administración. Dicha dosificación corresponde a 1.5 a 50 mg/kg por día. Convenientemente la dosis es de 5 a 20 mg/kg por día.

Un experto en la técnica reconocerá que la cantidad óptima y separación de las dosificaciones individuales de un compuesto de la invención se determinarán por medio de la naturaleza y el grado de la condición que se va a tratar, la forma, la vía y el sitio de la administración, y el mamífero particular que se va a tratar, y que dichos óptimos puede determinarse por técnicas convencionales. Un experto en la técnica también apreciará que el curso de tratamiento óptimo, es decir, el número de dosis de un compuesto de la invención que se da por día durante un número definido de días, puede ser determinado por los expertos en la técnica utilizando pruebas convencionales de determinación del curso de tratamiento.

La invención también se extiende a intermediarios novedosos descritos en la presente, utilizados en la preparación de compuestos de la fórmula (I) o sus sales.

Lo siguiente es una lista de las definiciones utilizadas:

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Definiciones

	APTS	ácido para toluen sulfónico
	AcOEt	etil acetato
	DCM	diclorometano
5	DIBAL-H	solución de hidruro de diisobutilaluminio
	DIPEA	diisopropiletilamina
	DME	1,2-dimetoxi etano
	DMF	dimetilformamida
	DMSO	dimetil sulfóxido
10	EDCI	clorhidrato de N3-(etilcarbonimidoil)-N1,N1-dimetilo- de 1,3-propanodiamina
	NEt ₃	triethylamina
	EtOH	etanol
	HATU	O-(7-Azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio
15	hexafluorofosfato	
	HCl	ácido clorhídrico
	HOBt	1-hidroxi benzotriazol
	NaOH	hidróxido de sodio
	NH ₄ Cl	cloruro de amonio
20	PBr ₃	tribromuro de fósforo
	Pd tetrakis	tetrakis(trifenilfosfina)paladio (0)
	Pd/C	paladio (0) sobre carbono
	TA	temperatura ambiente

15d

THF tetrahidrofurano

Independientemente de cómo se represente la preparación de compuestos en la especificación de la presente, ninguna conclusión puede representar que se utilizaron lotes particulares (o mezclas de dos o más lotes) de intermediarios en la siguiente etapa de la preparación. Los ejemplos e intermediarios pretenden ilustrar las vías sintéticas adecuadas para la preparación de los mismos, para ayudar a los expertos en la técnica a entender la presente invención.

En donde se hace referencia al uso de un procedimiento "similar", como lo apreciarán los expertos en la técnica, dicho procedimiento puede implicar menor variación, por ejemplo, temperatura de reacción, cantidad de reactivo/solvente, tiempo de reacción, condiciones de estudio o condiciones de purificación cromatográfica.

15 Métodos analíticos LC-MS

La HPLC analítica se realizó en una columna C18 X-terra MS (2.5 μ M 3 * 30 mm id) eluyendo con acetato de amonio 0.01M en agua (solvente A) y acetonitrilo al 100% utilizando la siguiente gradiente de elución: 0 a 4 minutos, 5 a 100 % B; 4 a 5 minutos, 100 % B a una velocidad de flujo de 1.1 mL/min con una temperatura de 40° C.

Los espectros de masa (MS) se registraron en un espectrómetro de masa ZQ-LC de micromasa que utiliza los modos de ionización positiva por electroaspersión [ES + ve para dar ion molecular MH^+] o ionización negativa

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por electroaspersión [ES-ve para dar ion molecular $(M-H)^-$].

Métodos analíticos LC-HRMS

La HPLC analítica se realizó en una columna Uptisphere-hsc (3
5 μm 30 * 3 mm id) eluyendo con acetato de amonio 0.01M en agua (solvente
A) y acetonitrilo al 100% (solvente B) utilizando la siguiente gradiente de
elución: 0 a 0.5 minutos, 5 % B; 0.5 a 3.5 minutos, 5 a 100 % B; 3.5 a 4
minutos, 100 % B; 4 a 4.5 minutos, 100 a 5 % B; 4.5 a 5.5 minutos, 5 % B a
una velocidad de flujo de 1.3 mL/min con una temperatura de 40° C.

10 Los espectros de masa (MS) se registraron en un espectrómetro
de masa LCT de micromasa que utiliza los modos de ionización positiva por
electroaspersión [ES + ve para dar ion molecular M^{H+}] o ionización negativa
por electroaspersión [ES-ve para dar ion molecular $(M-H)^-$].

15 Método analítico GC-MS

La GC analítica se realizó en una columna DB 1ms (Agilent
Technologies), 0.1 μm 10m * 0.1mm id) eluyendo con un flujo de Helio de
0.5ml/min y presión a 3.4 bar y con una temperatura de gradiente: 0 a 0.35
min, 100° C; 0.35min a 6 min, 100°C a 250°C (aumento gradual de la
20 temperatura de 80° C/min).

Los espectros de masa (MS) se registraron en un espectrómetro
de masa Agilent Technologies G5973 que utiliza ionización de impacto
electrónico.

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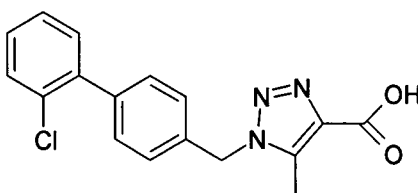
EJEMPLOS E INTERMEDIARIOS DE APOYO

La invención se ilustra por los Ejemplos no limitativos descritos más abajo.

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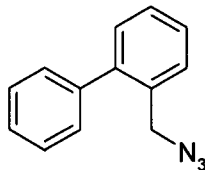
Intermediario 1: Acido 1-[(2'-Cloro-4-bifenilil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico

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A una solución de ácido 1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (0.2 g, 0.67 mmoles) en DME (10 mL) se le agregó ácido (2-clorofenil)borónico, (0.137g, 0.88 mmoles), Pd tetrakis (20 mg, 10% moles/moles) y una solución 2M de carbonato de sodio (1.34 mL, 4 eq). La
15 reacción se calentó a 85°C durante 48 horas. Después de la evaporación de DME, se agregó agua y la reacción se extrajo con etil acetato (2 X 40 ML). La fase acuosa se ajustó a pH = 7 por medio de la adición de una solución de HCl 1N y se extrajo con etil acetato. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron al vacío para dar el
20 compuesto del título como un sólido (117 mg, 40%). HRMS calculado para $C_{17}H_{14}ClN_3O_2$ (M + H)⁺ 328.0853, encontrado: 328.0865, TA: 2.04 min.

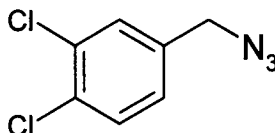
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Intermediario 2: azida de 2-bifenililmetilo

- 5 A una solución de 2-(bromometil)bifenilo (1.5 g, 6 mmoles) en DMSO (15 mL) se le agregó azida de sodio (0.59 g, 9 mmoles) y una cantidad catalítica de yoduro de sodio. La mezcla se agitó a temperatura ambiente durante 2 días. Después de la concentración bajo presión reducida, el residuo se diluyó con etil acetato. La capa orgánica se lavó con salmuera (2 X 60
- 10 ML), se secó en sulfato de sodio y después de filtrar se evaporó hasta secar para dar el compuesto del título como un aceite (1.1 g, 87%). ¹H RMN (300 MHz, CDCl₃, ppm) δ: 7.56-7.38 (m, 9H), 4.37 (s, 2H).

Intermediario 3: azida de (3,4-Diclorofenil)metilo

15



- Una mezcla de cloruro 3,4-diclorobencilo (10 G, 0.05 moles), azida de sodio (5 G, 0.08 moles) en DMSO (100 ML) se agitó a temperatura ambiente durante la noche. La mezcla se vertió en agua (150 mL). La capa de agua se extrajo con etil acetato (100 ml X 3). Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron al vacío. El residuo se purificó por destilación para dar el compuesto del título
- 20

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como un aceite (14 g, rendimiento cuantitativo). LC/MS: m/z 203 (M+H)⁺, TA: 2.26 min.

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Intermediario 3:

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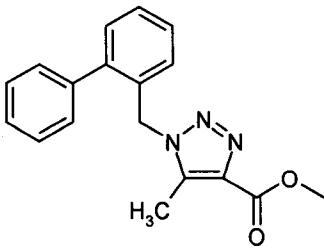
CUADRO 1

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Compuesto	Estructura	De	Datos físicos
Intermediario 4 (3,5-Diclorofenil) azida de metilo		cloruro 3,4-diclorobencilo	No aislado
Intermediario 5 (3-Clorofenil) azida de metilo		bromuro de 3 clorobencilo	LC/MS: m/z 168 (M+H) ⁺ , TA: 2.54 min

Intermediario 6: Metil 1-(2-bifenililmetil)-5-metil-1H-1,2,3-triazol-

15 4-carboxilato



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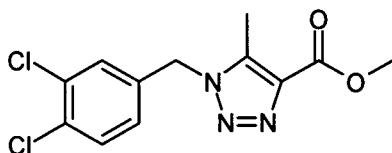
A una solución de azida de 2-bifenililmetilo (Intermediario 2) (1.1 g, 5.2 mmoles) y metil acetoacetato (0.9 g, 7.8 mmoles) en DMSO (10 mL) se le agregó carbonato de potasio (2.9 g, 20 mmoles). La mezcla de reacción se agitó a 40°C durante 48 horas. Después de enfriar, se agregó agua y la

[64]

mezcla se extrajo con etil acetato, la capa orgánica se secó en sulfato de sodio y después de filtrar se evaporó hasta secar. El residuo se purificó por cromatografía de columna instantánea eluyendo con DCM y DCM/MeOH: 98/2 para dar el compuesto del título como un aceite (1.1 g, 68.7%). LC/MS: m/z 308 (M+H)⁺, TA: 3.14 min.

Intermediario 7: Metil 1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxilato

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A una suspensión de carbonato de potasio molido (38.7 g, 0.28 moles) en DMSO (100 mL) se le agregó azida de (3,4-diclorofenil)metilo (Intermediario 3) (14 g, 0.07 moles) y metil acetoacetato (12.1 g, 0.1 moles). La mezcla se agitó a 40°C durante 48 horas. La mezcla se vertió en una mezcla de hielo y agua (100 mL). El agua se extrajo con etil acetato (100 ml X 2). Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó por destilación para dar el compuesto del título como cristales sólidos blancos (14 g, 67%). LC/MS: m/z 301 (M+H)⁺, TA: 1.97 min.

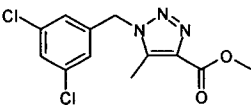
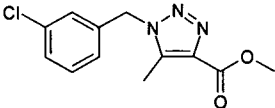
Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Intermediario 7:

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CUADRO 2

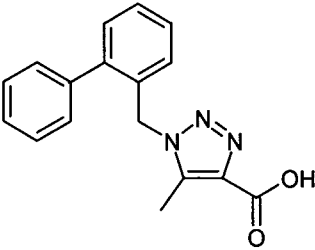
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Compuesto	Estructura	De	Datos físicos
Intermediario 8 Metil 1-[(3,5-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxilato		(3,5-Diclorofenil) azida de metilo (Intermediario 4)	LC/MS: m/z 300 (M+H) ⁺ , TA: 3.01 min
Intermediario 9 Metil 1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxilato		(3-Clorofenil) azida de metilo (Intermediario 5)	¹ H RMN (300 MHz, DMSO, ppm) δ: 7.39 (dd, 2H), 7.3 (s, 1H) 5.65 (s, 2H), 3.81 (s, 3H), 2.46 (s, 3H).

Intermediario 10: Acido 1-(2-Bifenililmetil)-5-metil-1H-1,2,3-triazol-4-carboxílico

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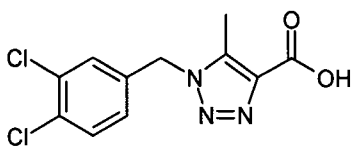
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A una solución de metil 1-(2-bifenililmetil)-5-metil-1H-1,2,3-triazol-4-carboxilato (Intermediario 6) (1.1 g, 3.58 mmoles) en metanol se le agregó una solución acuosa de hidróxido de sodio (7.2 mL, 6 mmoles). La solución se calentó a reflujo durante 3 horas. Después de la concentración bajo presión reducida, se agregó una solución de HCl 1N (8 mL). El material

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sólido resultante se filtró, se lavó con agua y se secó para dar el compuesto del título como un sólido cremoso (810 mg, 77%). LC/MS: m/z 294 (M+H)⁺, TA: 2.23 min.

5 Intermediario 11: Acido 1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico



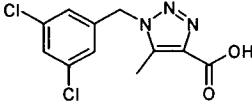
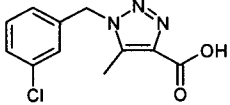
10 A una mezcla de metil 1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxilato (Intermediario 7) (9 g, 0.03 moles) en metanol (200 mL) se le agregó NaOH (2.4 g) y agua. La mezcla se agitó durante la noche. Se agregó agua y el solvente se evaporó. El residuo se extrajo con DCM (dos veces). La fase acuosa se ajustó a pH = 2 con una solución de HCl 2N. El

15 precipitado formado se filtró para dar el compuesto del título como un sólido blanco (7.29 g, 84%). LC/MS: m/z 287 (M+H)⁺, TA: 2.52 min.

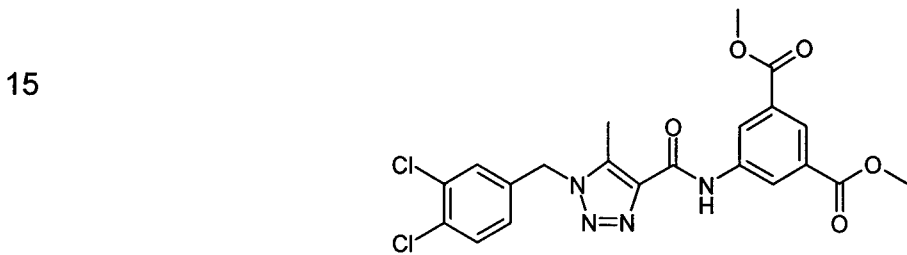
Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Intermediario 11:

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CUADRO 3

	Compuesto	Estructura	De	Datos físicos
5	Intermediario 12 1-[(3,5-Diclorofenil) Acido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico		Metil 1-[(3,5-diclorofenil) metil]-5-metil-1H-1,2,3-triazol-4-carboxilato (Intermediario 8)	LC/MS: m/z 286 (M+H) ⁺ , TA: 2.22 min
10	Intermediario 13 Acido 1-[(3-Clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico		Metil 1-[(3-clorofenil) metil]-5-metil-1H-1,2,3-triazol-4-carboxilato (Intermediario 9)	¹ H RMN (300 MHz, DMSO, ppm) δ: 7.37-7.27 (dd, 2H), 7.11 (s, 1H) 5.63 (s, 2H), 2.44 (s, 3H).

Intermediario 14: Dimetil 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-bencendicarboxilato



Una mezcla de ácido 1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) (0.4 g, 1.3 mmoles), dimetil 5-amino-1,3-bencendicarboxilato (0.29 g, 1 eq), HATU (0.69 g, 1,3 eq) y DIPEA (0.34 mL, 1.3 eq) en DMF (10 ML) se agitó a 45°C durante 24 horas. El solvente se evaporó y el residuo se lavó con agua y se extrajo con DCM. La fase orgánica se secó sobre sulfato de sodio y se concentró. El compuesto del título se

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obtuvo como un sólido blanco (650 mg, 95%) después de la recristalización de acetonitrilo. LC/MS: m/z 477 (M+H)⁺, TA: 3.81 min.

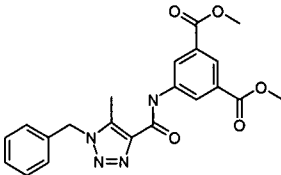
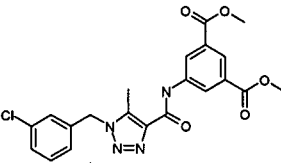
Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Intermediario 14:

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CUADRO 4

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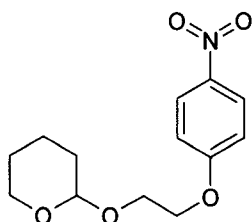
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Compuesto	Estructura	De	Datos físicos
Intermediario 15 Dimetil 5-([5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il]carbonil)amino)-1,3-bencendicarboxilato		Acido 5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxílico y dimetil 5-amino-1,3-benceno dicarboxilato	LC/MS: m/z 409 (M+H) ⁺ , TA: 3.34 min
Intermediario 16 Dimetil 5-([1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino)-1,3-bencendicarboxilato		Acido 1-[(3-Clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 13) y dimetil 5-amino-1,3-bencen dicarboxilato	LC/MS: m/z 443 (M+H) ⁺ , TA: 3.54 min

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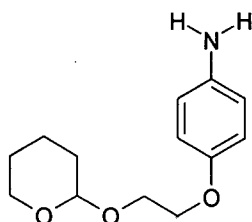
Intermediario 17: 2-({2-[(4-Nitrofenil)oxi]etil}oxi)tetrahidro-2H-pirano

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A una solución de 2-[(4-Nitrofenil)oxi]etanol (1 g, 5.4 mmoles), en tolueno (50 mL) se le agregó 3,4-dihidro-2H-pirano (1.5 mL) and APTS (cantidad catalítica). La reacción se agitó a 60°C durante 3 horas. La solución obscura entonces se concentró y se purificó por cromatografía instantánea utilizando DCM/ciclohexano 30/70 como eluyente. El compuesto del título se obtuvo como un aceite (1.33 g, 92%). LC: TA: 3.12 min.

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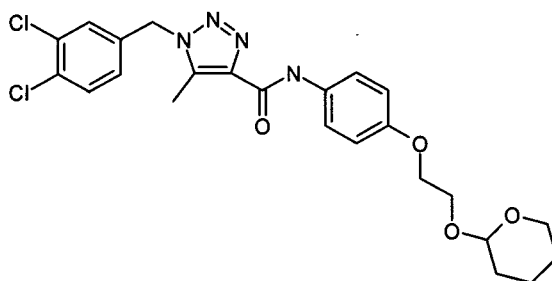
Intermediario 18: 4-({2-[(Tetrahidro-2H-piran-2-iloxi)etil]oxi}anilina

A una solución de 2-({2-[(4-nitrofenil)oxi]etil}oxi)tetrahidro-2H-pirano (Intermediario 17) (1.33 g, 5 mmoles) en EtOH (50 ML) se le agregó Pd/C (cantidad catalítica) y formiato de amonio (0.9 g, 10 eq). La reacción se agitó a 40°C durante 2 horas. Después de filtrar en celite, el solvente se evaporó y el residuo se vertió en agua, se extrajo con éter y se secó sobre

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sulfato de sodio y se evaporó. El compuesto del título se obtuvo como un aceite oscuro (0.8 g, 68%). LC/MS: m/z 238 ($M+H$)⁺, TA: 2.38 min.

- Intermediario 19: 1-[(3,4-Diclorofenil)metil]-5-metil-N-(4-{[2-(tetrahydro-2H-piran-2-iloxi)etil]oxi}fenil)-1H-1,2,3-triazol-4-carboxamida



- Una mezcla de ácido 1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) (0.3 g, 1 mmoles), 4-{[2-(tetrahydro-2H-piran-2-iloxi)etil]oxi}anilina (Intermediario 18) (0.28 g, 1.2 eq), HATU (0.8 g, 2 eq), y NEt₃ (440 μ L, 3 eq) en DMF se agitó a 45°C durante 18 horas. El solvente se evaporó y el residuo se lavó con agua y se extrajo con una mezcla de éter y etil acetato. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El compuesto del título se obtuvo y se utilizó en el siguiente paso sin purificación ni aislamiento.

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Intermediario 14:

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CUADRO 5

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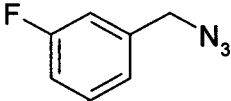
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Compuesto	Estructura	De	Datos físicos
Intermediario 20 Dimetil 4-([5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il]carbonil)amino)-1,2-bencendicarboxilato		ácido 5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxílico y dimetil 4-amino-1,2-bencendicarboxilato	LC/MS: m/z 407 (M-H) ⁺ , TA: 2.74 min
Intermediario 21 Dimetil 5-([1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino)-1,3-bencendicarboxilato		ácido 1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y dimetil 5-amino-1,3-bencendicarboxilato	LC/MS: m/z 427 (M+H) ⁺ , TA: 3.44 min
Intermediario 22 Dimetil 4-([1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino)-1,2-bencendicarboxilato		ácido 1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 13) y dimetil 4-amino-1,2-bencendicarboxilato	LC/MS: m/z 443 (M+H) ⁺ , TA: 3.36 min
Intermediario 23 Dimetil 4-([1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino)-1,2-bencendicarboxilato		ácido 1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y dimetil 4-amino-1,2-bencendicarboxilato	LC/MS: m/z 427 (M+H) ⁺ , TA: 3.22 min

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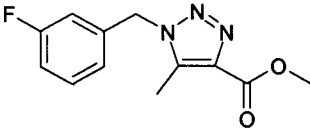
El siguiente compuesto se preparó de igual manera por medio de un método análogo al que se describió para el Intermediario 3:

CUADRO 6

5	Compuesto	Estructura	De	Datos físicos
	Intermediario 24 (3-fluorofenil) azida de metilo		bromuro de 3-fluorobencilo	No aislado

10 El siguiente compuesto se preparó de igual manera por medio de un método análogo al que se describió para el Intermediario 7:

CUADRO 7

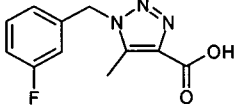
15	Compuesto	Estructura	De	Datos físicos
	Intermediario 25 Metil 1-[(3-fluorofenil) metil]-5-metil-1H-1,2,3-triazol-4-carboxilato		(3-fluorofenil) azida de metilo (Intermediario 24)	LC/MS: m/z 250 (M+H) ⁺ , TA: 2.61 min

20 El siguiente compuesto se preparó de igual manera por medio de un método análogo al que se describió para el Intermediario 11:

123

CUADRO 8

5

Compuesto	Estructura	De	Datos físicos
Intermediario 26 ácido 1-[(3-Fluorofenil)metil]-5-metil-1 <i>H</i> -1,2,3-triazol-4-carboxílico		metil 1-[(3-fluorofenil)metil]-5-metil-1 <i>H</i> -1,2,3-triazol-4-carboxilato (Intermediario 25)	LC/MS: m/z 236 (M+H) ⁺ , TA: 1.56 min

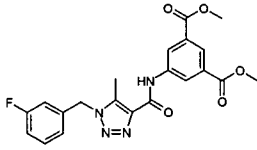
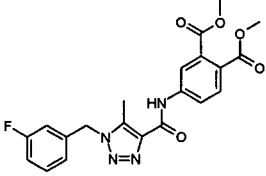
Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Intermediario 14:

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CUADRO 9

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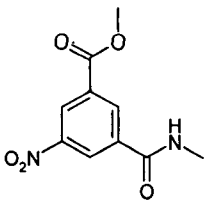
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Compuesto	Estructura	De	Datos físicos
Intermediario 27 Dimetil 5-[(1-[(3-fluorofenil)metil]-5-metil-1 <i>H</i> -1,2,3-triazol-4-il)carbonil)amino]-1,3-bencendicarboxilato		ácido 1-[(3-fluorofenil)metil]-5-metil-1 <i>H</i> -1,2,3-triazol-4-carboxílico (Intermediario 26) y dimetil 5-amino-1,3-bencendicarboxilato	LC/MS: m/z 427 (M+H) ⁺ , TA: 3.35 min
Intermediario 28 Dimetil 4-[(1-[(3-fluorofenil)metil]-5-metil-1 <i>H</i> -1,2,3-triazol-4-il)carbonil)amino]-1,2-bencendicarboxilato		ácido 1-[(3-fluorofenil)metil]-5-metil-1 <i>H</i> -1,2,3-triazol-4-carboxílico (Intermediario 26) y dimetil 5-amino-1,2-bencendicarboxilato	LC/MS: m/z 427 (M+H) ⁺ , TA: 3.21 min

PM

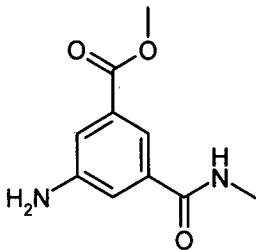
El siguiente compuesto se preparó de igual manera por medio de un método análogo al que se describió para el Intermediario 19:

CUADRO 10

5	Compuesto	Estructura	De	Datos físicos
	Intermediario 29		ácido 3-[(metiloxi) carbonil] -5-nitrobenzoico y metilamina	LC/MS: m/z 239 (M+H) ⁺ , TA: 2.26 min

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Intermediario 30: Metil 3-amino-5-[(metilamino)carbonil]benzoato



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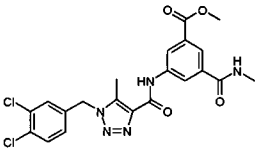
A una solución de metil 3-[(metilamino)carbonil]-5-nitrobenzoato (Intermediario 29) (1.33 g, 5.59 mmoles), en etanol (30 mL) se le agregaron formiato de amonio (3.52 g, 1eq.) y Pd/C (cantidad catalítica). La reacción se agitó a 40°C durante una noche. Después de la filtración sobre celite, el solvente se evaporó al vacío. El residuo se disolvió en DCM, se lavó con agua, se secó sobre sulfato de sodio y se concentraó para dar el compuesto del título como un sólido blanco (0.56 g, 48.3%). LC/MS: m/z 209 (M+H)⁺, TA: 1.50 min.

20

MS

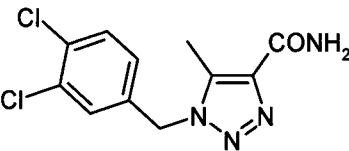
El siguiente compuesto se preparó de igual manera por medio de un método análogo al que se describió para el Intermediario 14:

CUADRO 11

5	Compuesto	Estructura	De	Datos físicos
10	Intermediario 31. Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-5-[(metilamino) carbonil] benzoato		ácido 1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) y metil 3-amino-5-[(metilamino) carbonil] benzoato (Intermediario 30)	LC/MS: m/z 476 (M+H)+, TA: 3.15 min

Intermediario 32: 1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida

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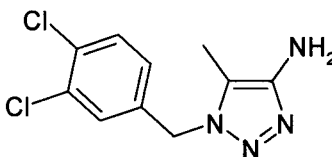
A una solución de ácido (1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico) (Intermediario 11) (14 g, 48.93 mmoles), en cloroformo (200 mL) se le agregó cloruro de tionilo (30 mL) a temperatura ambiente. La mezcla de reacción se agitó a reflujo durante 4 horas y se concentró al vacío. La mezcla entonces se disolvió en acetonitrilo (50 mL) y se agregó amoniaco acuoso (50 mL) a 0°C durante 30 min. El sólido

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resultante se filtró y se secó para dar el compuesto del título como cristales blancos. (12.7 g, 91.1%). LC/MS: m/z 285 (M+H)⁺, TA: 2.53 min.

Intermediario 33: 1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-

5 triazol-4-amina

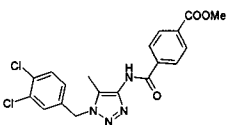


A una solución de hidróxido de potasio (10.96 g, 195.8 mmoles) en agua (50 mL) enfriada en un baño de hielo-sal, se le agregó bromuro (6.3 g, 32.16 mmoles) y a 0° C, se agregó 1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida (Intermediario 32) (9.3 g, 32.63 mmoles) durante 4 horas bajo agitación vigorosa. La mezcla de reacción entonces se calentó a 80°C durante 2 días y se agitó a temperatura ambiente durante 12 horas. El sólido resultante se filtró y se purificó por HPLC para dar el compuesto del título (3.45 g, 41.14%). LC/MS: m/z 257 (M+H)⁺. TA: 2.25 min.

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Intermediario 14:

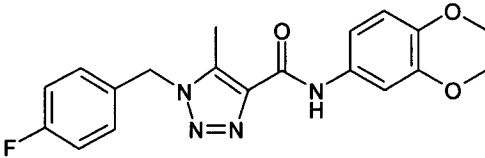
177

CUADRO 12

Compuesto	Estructura	De	Datos físicos
Intermediario 34 Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)amino)carbonil]benzoato		1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-amina (Intermediario 33) y ácido 4-[(metiloxi)carbonil]benzoico	LC/MS: m/z 419 (M+H)+, TA: 3.11 min

EJEMPLO 1

N-[3,4-bis(Metiloxi)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida



Una mezcla de ácido 1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (0.2 g, 0.85 mmoles), 3,4-bis(metiloxi)anilina (0.156 g, 1.2 eq), HATU (0.485 g, 1.5 eq) y DIPEA (240 µL, 1.5 eq) en DMF se agitó a temperatura ambiente durante la noche. El solvente se evaporó y el residuo se lavó con agua y se extrajo con DCM. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó por cromatografía de columna instantánea eluyendo con DCM para dar después de la precipitación del éter, el compuesto del título como un sólido blanco (180

178

mg, 57%). HRMS calculado para C₁₉H₁₉FN₄O₃ (M+H)⁺ 371.1519, encontrado: 371.1500, TA: 2.78 min. PF: 119.7□

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 1:

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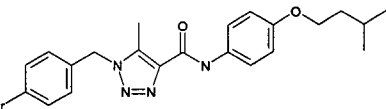
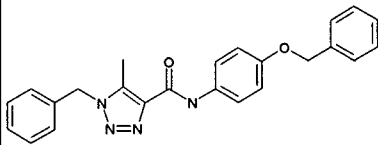
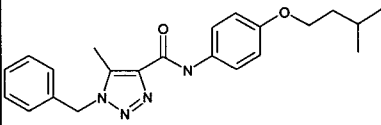
CUADRO 13

Compuesto	Estructura	De	Datos físicos
Ejemplo 2 N-[3,4-bis(metiloxi)fenil]-1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y 3,4-bis(metiloxi)anilina	RMS calculado para C₁₉H₁₉BrN₄O₃ teórico: 431.0719 encontrado: 431.0684 TA: 2.93 min. PF: 173□
Ejemplo 3 1-[(4-bromofenil)metil]-5-metil-N-{4-[(fenilmetil)oxi]fenil}-		ácido 1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y 4-[(fenilmetil)oxi] anilina	RMS calculado para C₂₄H₂₁BrN₄O₂ teórico: 477.0926 encontrado: 477.0963

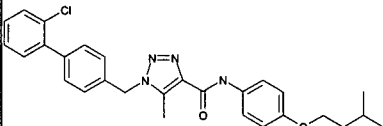
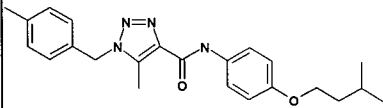
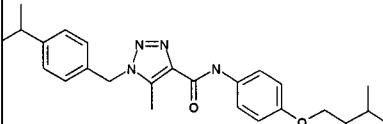
179

Compuesto	Estructura	De	Datos físicos
1H-1,2,3-triazol-4-carboxamida			A: 3.49 min. F: 168.7□
Ejemplo 4 1-[(4-Fluorofenil)metil]-5-metil-N-{4-(fenilmetil)oxi}fenil}-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y 4-[(fenilmetil)oxi] anilina	RMS calculado para $C_{24}H_{21}FN_4O_2$ es: 417.1727 encontrado: 417.1768 A: 3.32 min. F: 139.4□
Ejemplo 5 1-[(4-Fluorofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y 4-[(3-metilbutil)oxi] anilina	RMS calculado para $C_{22}H_{25}FN_4O_2$ es: 397.2040 encontrado: 397.2061 A: 3.58 min F: 114□

180

Compuesto	Estructura	De	Datos físicos
Ejemplo 6 1-[(4-bromofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y 4-[(3-metilbutil)oxi] anilina	RMS calculado para $C_{22}H_{25}BrN_4O_2$ eo: 457.1239 encontrado: 57.1256 A: 3.76 min F: 137°
Ejemplo 7 5-Metil-1-(fenilmetil)-N-{4-(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida		ácido 5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxílico y 4-[(fenilmetil)oxi] anilina	RMS calculado para $C_{24}H_{22}N_4O_2$ eo: 399.1821 encontrado: 99.1819 A: 3.34 min F: 125°
Ejemplo 8 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida		ácido 5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxílico y 4-[(3-metilbutil)oxi] anilina	RMS calculado para $C_{22}H_{26}N_4O_2$ eo: 379.2134 encontrado: 79.2165

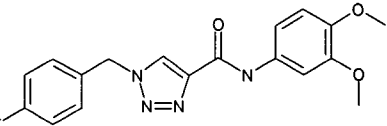
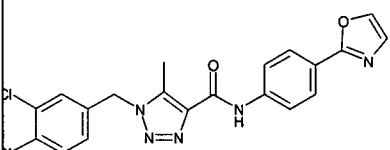
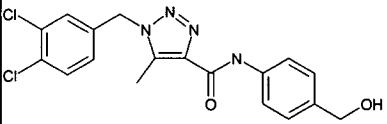
181

Compuesto	Estructura	De	Datos físicos
1H-1,2,3-triazol-4-carboxamida			A: 3.55 min F: 124□
Ejemplo 9 1-[(2-bromofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(2'-Cloro-4-fenilil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 1) 4-[(3-metilbutil)oxi]anilina	RMS calculado para $C_{28}H_{29}ClN_4O_2$ eo: 489.2057 ncontrado: 39.2104 A: 3.99 min F: >125□ (descomposición)
Ejemplo 10 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxamida,		ácido 5-metil-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxílico 4-[(3-metilbutil)oxi]anilina	RMS calculado para $C_{23}H_{28}N_4O_2$ eo: 393.2290 ncontrado: 93.2285 A: 3.70 min F: 105□
Ejemplo 11 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-(1-metiletil)fenil]metil]-1H-1,2,3-triazol-4-carboxamida,		ácido 5-metil-1-[(1-metiletil)fenil]metil]-1H-1,2,3-triazol-4-carboxílico	RMS calculado para $C_{25}H_{32}N_4O_2$ eo: 421.2603

182

Compuesto	Estructura	De	Datos físicos
metilbutil)oxi] fenil}-1-{{4-(1- netiletil)fenil]metil}- 1H-1,2,3-triazol-4- carboxamida		1H-1,2,3-triazol-4- carboxílico y 4-[(3- metilbutil)oxi] anilina	ncontrado: 21.2585 A: 3.93 min F: >114° (descomposición)
Ejemplo 12 N-[3,4-bis(metiloxi) fenil]-5-metil- 1-[(4-metilfenil) metil]-1H-1,2,3- triazol-4- carboxamida		ácido 5-metil-1-[(4- metilfenil)metil]-1H- 1,2,3-triazol-4- carboxílico y 3,4- bis(metiloxi) anilina	RMS calculado para C ₂₀ H ₂₂ N ₄ O ₃ eo: 367.1770 ncontrado: 67.1751 A: 2.88 min F: >156° (descomposición)
Ejemplo 13 (2-Bifenililmetil)-N- [3,4-bis(metiloxi) fenil]-5-metil-1H- 1,2,3-triazol-4- carboxamida		ácido 1-[(2- diclorofenil)metil]-5- metil-1H-1,2,3- triazol-4-carboxílico Intermediario 10) y 3,4-bis(metiloxi) anilina	RMS calculado para C ₂₅ H ₂₄ N ₄ O ₃ eó. 429.1927 ncontrado: 29.1937 A: 3.2 min F: 121°

183

Compuesto	Estructura	De	Datos físicos
Ejemplo 14 N-[3,4-bis(metiloxi)fenil]-1-[(4-fluorofenil)metil]-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(4-fluorofenil)metil]-1H-1,2,3-triazol-4-carboxílico y 3,4-bis(metiloxi)anilina	RMS calculado para C₁₈H₁₇N₄O₃ teó. 357.1363 encontrado: 357.1355 A: 2.55 min F: 197.8°
Ejemplo 15 1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1,3-oxazol-2-il)fenil]-1H-1,2,3-triazol-4-carboxamida,		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) y 4-(1,3-oxazol-2-il)anilina	RMS calculado para C₂₀H₁₅Cl₂N₅O₂ teo: 428.0681 encontrado: 428.0716 A: 3.14 min. F: 218°
Ejemplo 16 1-[(3,4-Diclorofenil)metil]-N-[4-hidroximetil]fenil]-5-metil-1H-1,2,3-		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) y	RMS calculado para C₁₈H₁₆Cl₂N₄O₂ teo: 391.0728 encontrado: 391.0755

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Compuesto	Estructura	De	Datos físicos
triazol-4-carboxamida		(4-aminofenil) metanol	A: 2.77 min F: 183□
Ejemplo 17 Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]-3-(metiloxi)benzoato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) y metil 4-amino-3-(metiloxi)benzoato	RMS calculado para $C_{20}H_{18}Cl_2N_4O_4$ eo: 449.0783 ncontrado: 49.0813 A: 3.42 min F: 212□
Ejemplo 18 1-[(3,4-Diclorofenil)metil]-5-metil-N-{3-[(metilamino)carbonil]fenil}-1H-1,2,3-triazol-4-carboxamida		metil 1-(2-fenililmetil)-5-metil-1H-1,2,3-triazol-4-carboxilato (Intermediario 6) y 3-amino-N-metilbenzamida	RMS calculado para $C_{19}H_{17}Cl_2N_5O_2$ eo: 418.0837 ncontrado: 18.0851 A: 2.74 min F: 203.9□

185

Compuesto	Estructura	De	Datos físicos
Ejemplo 19 1-[(3,4-Diclorofenil)metil]-5-metil-N-{4-[(metilamino)carbonil]fenil}-1H-1,2,3-triazol-4-carboxamida		1-[(3,4-diclorofenil)acido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) y 4-amino-N-metilbenzamida	RMS calculado para $_{19}\text{H}_{17}\text{Cl}_2\text{N}_5\text{O}_2$ eo: 418.0837 encontrado: 418.0839 A: 2.71 min F: 183.7°
Ejemplo 20 Etil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoato		1-[(3,4-diclorofenil)acido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) y etil 3-aminobenzoato	RMS calculado para $_{20}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_3$ eo: 433.0834 encontrado: 433.0797 A: 3.38 min F: 131.8°
Ejemplo 21 N-3-[Acetilamino]fenil]-1-[(3,4-diclorofenil)metil]-5-		1-[(3,4-diclorofenil)acido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11)	RMS calculado para $_{19}\text{H}_{17}\text{Cl}_2\text{N}_5\text{O}_2$ eo: 418.0837 encontrado:

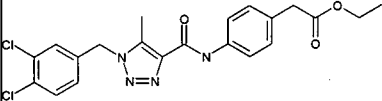
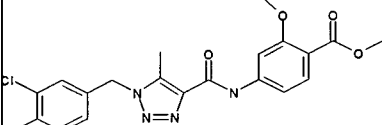
80

Compuesto	Estructura	De	Datos físicos
metil-1H-1,2,3-triazol-4-carboxamida		y N-[(3-aminofenil) acetamida	18.0830 A: 2.78 min F: 203.4□
Ejemplo 22 N-4-[Acetilamino) fenil]-1-[(3,4-diclorofenil) metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1-[(3,4-diclorofenil) ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y N-(4-aminofenil) acetamida	RMS calculado para $C_{19}H_{17}Cl_2N_5O_2$ Teo: 418.0837 Encontrado: 18.0840 A: 2.72 min F: 202.4□
Ejemplo 23 1-[(3,4-Diclorofenil) metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1-[(3,4-diclorofenil) ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y 3-amino-2-metilfenil) metanol	RMS calculado para $C_{19}H_{18}Cl_2N_4O_2$ Teo: 405.0885 Encontrado: 05.0878 A: 2.78 min F: 174.3□
Ejemplo 24		1-[(3,4-diclorofenil) ácido metil]-5-metil-	RMS calculado para

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Compuesto	Estructura	De	Datos físicos
1-[(3,4-Diclorofenil)metil]-N-[3-hidroximetil]fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1H-1,2,3-triazol-4-carboxílico Intermediario 11) y (3-aminofenil) metanol	$C_{18}H_{16}Cl_2N_4O_2$ eo: 391.0728 ncontrado: 91.0695 A: 2.78 min F: 185.2
Ejemplo 25 Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]-4-(metiloxi) benzoato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y metil 3-amino-4-(metiloxi) benzoato	RMS calculado ara $C_{20}H_{18}Cl_2N_4O_4$ eo: 449.0783 ncontrado: 49.0802 A: 3.36 min F: 203
Ejemplo 26 1-[(3,4-Diclorofenil)metil]-N-[4-hidroxi-3-(hidroximetil)fenil]-5-metil-1H-		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y 4-amino-2-	RMS calculado ara $C_{18}H_{16}Cl_2N_4O_3$ eo: 407.0677 ncontrado: 07.0683

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Compuesto	Estructura	De	Datos físicos
1,2,3-triazol-4-carboxamida		(hidroximetil) fenol	A: 2.57 min F: 175.6□
Ejemplo 27 Etil {4-[(1-(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]frenil}acetato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y etil (4-aminofenil) acetato	RMS calculado para $C_{21}H_{20}Cl_2N_4O_3$ Teo: 447.0990 Encontrado: 47.0975 A: 3.25 min F: 139□
Ejemplo 28 Metil 4-[(1-(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]-2-(metiloxi) benzoato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y metil 4-amino-2-(metiloxi) benzoato	RMS calculado para $C_{20}H_{18}Cl_2N_4O_4$ Teo: 449.0783 Encontrado: 49.0787 A: 3.1 min F: 175.9□

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Compuesto	Estructura	De	Datos físicos
Ejemplo 29 Metil 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]-2-hidroxibenzoato		1-[(3,4-diclorofenil)acido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y metil 5-amino-2-hidroxibenzoato	RMS calculado para $C_{19}H_{16}Cl_2N_4O_4$ es: 435.0627 Encontrado: 435.0638 TA: 3.2 min FP: 180 °C
Ejemplo 30 Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]fenil}acetato		1-[(3,4-diclorofenil)acido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y metil (3-aminofenil)acetato	RMS calculado para $C_{20}H_{18}Cl_2N_4O_3$ es: 433.0834 Encontrado: 433.0825 TA: 3.14 min FP: 116 °C
Ejemplo 31 1-[(3,4-Diclorofenil)metil]-N-(3-hidroxifenil)-5-metil-		1-[(3,4-diclorofenil)acido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11)	RMS calculado para $C_{17}H_{14}Cl_2N_4O_2$ es: 377.0572 Encontrado:

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Compuesto	Estructura	De	Datos físicos
1H-1,2,3-triazol-4-carboxamida		y 3-aminofenol	77.0593 A: 2.86 min F: 192.5□
Ejemplo 32 Metil 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]-2-fluorobenzoato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y metil 5-amino-2-fluorobenzoato	RMS calculado para $C_{19}H_{15}Cl_2N_4O_3$ Teo: 437.0583 Encontrado: 37.0544 A: 3.22 min F: 169.8□
Ejemplo 33 N-[5-(Aminocarbonil)-2-(metiloxi)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y -amino-4-(metiloxi)benzamida	RMS calculado para $C_{19}H_{17}Cl_2N_5O_3$ Teo: 434.0786 Encontrado: 34.0773 A: 2.77 min F: 218.2□

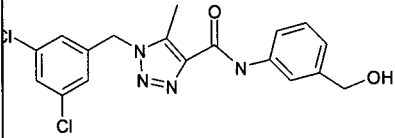
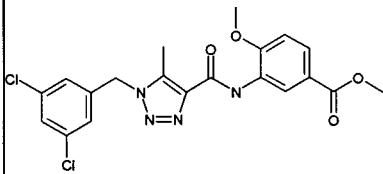
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Compuesto	Estructura	De	Datos físicos
Ejemplo 34 meti 4-cloro-3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y metil 3-amino-4-clorobenzoato	RMS calculado para $^{19}\text{H}_{15}\text{Cl}_3\text{N}_4\text{O}_3$ eo: 453.0288 encontrado: 53.0330 A: 3.59 min F: 206.4°
Ejemplo 35 Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]-4-(metiloxi)frenil]acetato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y metil [3-amino-4-(metiloxi)frenil]acetato	RMS calculado para $^{21}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_4$ eo: 463.0940 encontrado: 63.0985 A: 3.29 min F: 133°
Ejemplo 36 Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carbonil)amino]-4-(metiloxi)frenil]acetato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico	RMS calculado para $^{19}\text{H}_{15}\text{Cl}_2\text{N}_4\text{O}_3$ eo: 437.0583

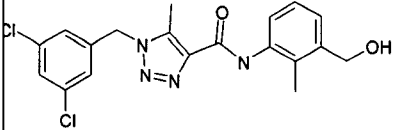
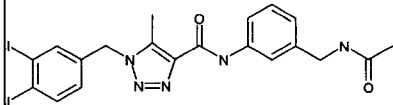
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Compuesto	Estructura	De	Datos físicos
metil]-5-metil-1H-1,2,3-triazol-4-(carbonil)amino]-4-fluorobenzoato		Intermediario 11) y metil 3-amino-4-fluorobenzoato	ncontrado: 37.0624 A: 3.37 min F: 195.7°
Ejemplo 37 N-[3-(Hidroximetil)fenil]-5-metil-1-enilmetil)-1H-1,2,3-triazol-4-carboxamida		ácido 5-metil-1-enilmetil)-1H-1,2,3-triazol-4-carboxílico (comercialmente disponible) y (3-aminofenil) metanol	RMS calculado para C ₁₈ H ₁₈ N ₄ O ₂ eo: 323.1508 ncontrado: 23.1529 A: 2.45 min F: 105.8°
Ejemplo 38 N-[4-(Hidroximetil)fenil]-5-metil-1-enilmetil)-1H-1,2,3-triazol-4-carboxamida		ácido 5-metil-1-enilmetil)-1H-1,2,3-triazol-4-carboxílico (comercialmente disponible) y (4-aminofenil) metanol	RMS calculado para C ₁₈ H ₁₈ N ₄ O ₂ eo: 323.1508 ncontrado: 23.1504 A: 2.42 min F: 149.1°
Ejemplo 39 -[3-(hidroximetil)-2-		ácido 5-metil-1-enilmetil)-1H-1,2,3-triazol-4-carboxílico	RMS calculado para C ₁₉ H ₂₀ N ₄ O ₂ eo: 337.1664

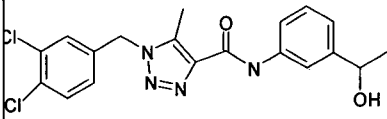
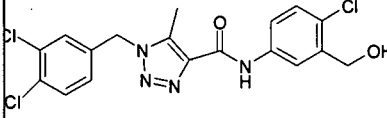
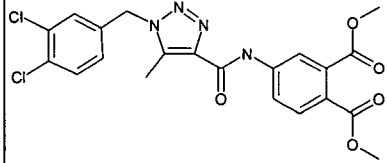
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Compuesto	Estructura	De	Datos físicos
metilfenil]-5-metil-1- enilmetil)-1H-1,2,3- triazol-4- carboxamida		(comercialmente disponible) y (3-amino-2- metilfenil) metanol	ncontrado: 37.1654 A: 2.44 min F: 157□
Ejemplo 40 1-[(3,5-Diclorofenil) metil]-N-[3- (hidroximetil) fenil]-5-metil-1H- 1,2,3-triazol-4- carboxamida		1-[(3,5-diclorofenil) ácido metil]-5-metil- 1H-1,2,3-triazol-4- carboxílico (Intermediario 12) y (3-aminofenil) metanol	RMS calculado ara 18H ₁₆ Cl ₂ N ₄ O ₂ eo: 391.0728 ncontrado: 91.0726 A: 2.84 min F: 159□
Ejemplo 41 Metil 3-[(1-[(3,5- diclorofenil) metil]-5-metil-1H- 1,2,3-triazol-4- carbonil)amino]-4- (metiloxi)		1-[(3,5-diclorofenil) ácido metil]-5-metil- 1H-1,2,3-triazol-4- carboxílico Intermediario 12) y metil 3-amino-4- (metiloxi) benzoato	RMS calculado ara 20H ₁₈ Cl ₂ N ₄ O ₄ eo: 449.0783 ncontrado: 49.0783 A: 3.44 min F: 213□

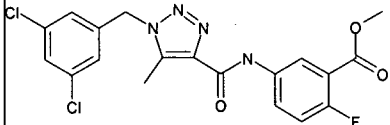
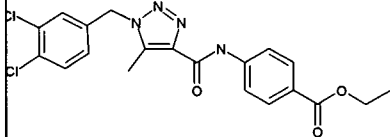
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Compuesto	Estructura	De	Datos físicos
benzoato			
Ejemplo 42 -[(3,5-Diclorofenil) metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1-[(3,5-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 12) y -amino-2-metilfenil)metanol	RMS calculado ara 19H ₁₈ Cl ₂ N ₄ O ₂ eo: 405.0885 ncontrado: 05.0860 A: 2.83 min F: 185□
Ejemplo 43 N 3-[Acetilamino)metil]fenil)-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 11) y N-[(3-aminofenil)metil]acetamida	RMS calculado ara 20H ₁₉ Cl ₂ N ₅ O ₂ eo: 432.0994 ncontrado: 32.1003 A: 2.83 min F: 188.4□

15

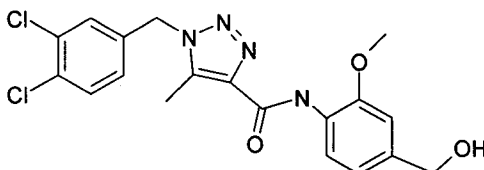
Compuesto	Estructura	De	Datos físicos
Ejemplo 44 1-[(3,4-Diclorofenil)metil]-N-[3-(1-hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1-[(3,4-diclorofenil)metil]-N-[3-(1-hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y 1-(3-aminofenil) etanol	RMS calculado para $C_{19}H_{18}Cl_2N_4O_2$ teo: 405.0885 encontrado: 405.0869 A: 2.97 min F: 145°
Ejemplo 45 N-[4-Cloro-3-(hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		1-[(3,4-diclorofenil)metil]-N-[4-Cloro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y (5-amino-2-clorofenil) metanol	RMS calculado para $C_{18}H_{15}Cl_3N_4O_2$ teo: 425.0339 encontrado: 425.0315 A: 3.12 min F: 190.3°
Ejemplo 46 Dimetil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxilato)]benzoato		1-[(3,4-diclorofenil)metil]-N-[4-(dimetilcarboxilato)fenil]-5-metil-1H-1,2,3-triazol-4-carboxílico	RMS calculado para $C_{21}H_{18}Cl_2N_4O_5$ teo: 477.0732

lab

Compuesto	Estructura	De	Datos físicos
metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-1,2-bencen dicarboxilato		Intermediario 11) y dimetil 4-amino-1,2-bencen dicarboxilato	ncontrado: 77.0703 A: 3.23 min F: 148□
Ejemplo 47 Metil 5-[(1-[(3,5-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-fluorobenzoato		1-[(3,5-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 12) y metil 5-amino-2-fluorobenzoato	RMS calculado para $C_{19}H_{15}Cl_2N_4O_3$ eo: 437.0583 ncontrado: 37.0562 A: 3.29min F: 191□
Ejemplo 48 Etil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]benzoato		1-[(3,4-diclorofenil)ácido metil]-5-metil-1H-1,2,3-triazol-4-carboxílico Intermediario 11) y dimetil 4-aminobenzoato	RMS calculado para $C_{20}H_{18}Cl_2N_4O_3$ eo: 433.0834 ncontrado: 33.0830 A: 3.37 min F: 167□

EJEMPLO 49

1-[(3,4-Diclorofenil)metil]-N-[4-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida



5

A una solución de metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-3-(metiloxi)benzoato (Ejemplo 17) (0.1 g, 0.2 mmoles) en THF se agregó a 1M de solución de DIBAL-H en THF (800 μ L, 4 eq) y la reacción se agitó a temperatura ambiente por 2 horas. Se agregó NH_4Cl sólido después de agua y una solución de 1N HCl. La fase acuosa se extrajo con éter y AcOEt, secos sobre sulfato de sodio y se evaporó. El compuesto del título se obtuvo como un sólido blanco (30 mg, 35%) después de la recristalización de acetonitrilo. HRMS calculado para $\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_3$ (M+H)⁺ 421.0834, encontró: 421.0834, TA: 2.94 min. PF: 136 $^\circ$

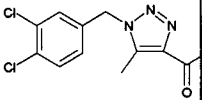
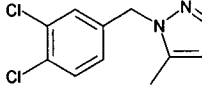
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Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 49:

CUADRO 14

20

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Comp uesto	Estructura	De	Dat os físicos
Ejempl o 50 1- [(3,4-Diclorofenil) metil]- N-[4-(2-hidroxietil) fenil]- 5-metil-1H-1,2,3- triazol-4- carboxamida		Etil {4-[(1-[(3,4- diclorofenil) metil]- 5-metil-1H-1,2,3- triazol-4-il} carb onil)amino] frenil }acetato EJE MPLO 27	HR MS calculado para C₁₉H₁₈Cl₂N₄O₂ Te o: 405.0885 En contrado: 405.0885 TA: 2.79 min. PF: 144□
Ejempl o 51 1- [(3,4-Diclorofenil) metil]- N-[5-(hidroximetil)-		Metil 3-[(1-[(3,4- diclorofenil) metil]- 5-meti-1H-1,2,3- triazol-4- i]carbonil)amino]-	HR MS calculado para C₁₉H₁₈Cl₂N₄O₃ Te o: 421.0834 En

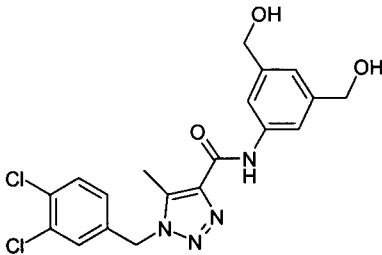
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Comp uesto	Estructura	De	Dat os físicos
2-(metiloxi)fenil]-5- metil-1H-1,2,3- triazol-4- carboxamida		4-(metiloxi) benz oato (Ejemplo 25)	contrado: 421.0794 TA: 2.91 min. PF: 198□

EJEMPLO 52

N-[3,5-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-
triazol-4-carboxamida

5



A una solución de dimetil 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-bencendicarboxilato (Intermedio 14)
10 (0.65 g, 1.3 mmoles) en THF (40 mL), se agregó a 1M de solución de DIBAL-H en tolueno (10 µL, 7 eq) y la reacción se agitó a temperatura ambiente por 2 horas. Se agregó NH₄Cl sólido y la mezcla de reacción se agitó a TA por 30

min. La fase acuosa se extrajo con éter y AcOEt, se secó sobre sulfato de sodio y se evaporó. El compuesto del título se obtuvo como un sólido blanco (240 mg, 44%) después de la recristalización de acetonitrilo. HRMS calculado para $C_{19}H_{18}Cl_2N_4O_3$ $(M+H)^+$ 421.0834, encontró: 421.0833, TA: 2.51 min. PF:

5 194.5□

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 49:

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CUADRO 15

Compuesto	Estructura	De	Datos fisicos
Ejemplo 53 1-[(3,4-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		metil 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-2-fluorobenzoato(Example 32)	HRMS calculado para C ₁₈ H ₁₅ Cl ₂ N ₄ O ₂ Teo: 409.0634 Encontrado: 409.0617 TA: 2.87 min. PF: 189.7°
Ejemplo 54 1-[(3,4-Diclorofenil)metil]-N-[5-(2-hidroxietil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		metil [3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-4-(metiloxi)fenil]acetato EJEMPLO 35	HRMS calculado para C ₂₀ H ₂₀ Cl ₂ N ₄ O ₃ Teo: 435.0991 Encontrado: 435.0975 TA: 3.01 min. PF: 138°
Ejemplo 55 1-[(3,4-Diclorofenil)metil]-N-[2-fluoro-5-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-4-fluorobenzoato(Example 36)	HRMS calculado para C ₁₈ H ₁₅ Cl ₂ N ₄ O ₂ Teo: 409.0634 Encontrado: 409.0624 TA: 2.92 min. PF: 210.5°
Ejemplo 56 N-[2-Cloro-5-(hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		metil 4-cloro-3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoato EJEMPLO 34	HRMS calculado para C ₁₈ H ₁₅ Cl ₃ N ₄ O ₂ Teo: 425.0339 Encontrado: 425.0339 TA: 3.11 min. PF: 220°

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Ejemplo 57 1-[(3,5-Diclorofenil)metil]-N-[5-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		metil 3-[(1-[(3,5-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-4-(metiloxi)benzoato EJEMPLO 41	HRMS calculado para $C_{19}H_{18}Cl_2N_4O_3$ Teo: 421.0834 Encontrado: 421.0807 TA: 2.99 min. PF: 214□
Ejemplo 58 N-[3,4-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		dimetil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,2-bencen dicarboxilato (Ejemplo 46)	HRMS calculado para $C_{19}H_{18}Cl_2N_4O_3$ Teo: 421.0834 Encontrado: 421.0875 TA: 2.60 min. PF: 203□
Ejemplo 59 1-[(3,5-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		metil 5-[(1-[(3,5-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-2-fluorobenzoato o EJEMPLO 47	HRMS calculado para $C_{18}H_{15}Cl_2N_4O_2$ Teo: 409.0634 Encontrado: 409.0630 TA: 2.92 min. PF: 178□
Ejemplo 60 N-[3,5-bis(Hidroximetil)fenil]-5-metil-1-[(3,4-diclorofenil)metil]-1H-1,2,3-triazol-4-carboxamida		dimetil 5-[(5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-bencen dicarboxilato	HRMS calculado para $C_{19}H_{20}N_4O_3$ Teo: 353.1613 Encontrado: 353.1600 TA: 2.99 min. PF: 214□

203

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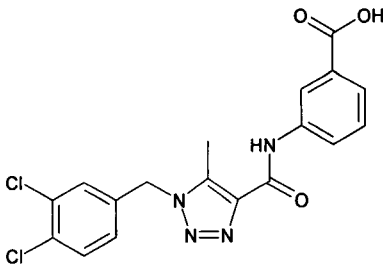
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Ejemplo 61 -[3,5-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		dimetil 5-[(1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-benzen dicarboxilato (Intermediario 16)	HRMS calculado para C₁₉H₁₉ClN₄O₃ Teo: 387.1224 Encontrado: 387.1198 TA: 2.37 min. PF: 192.7°
Ejemplo 62 1-[(3,4-Diclorofenil)metil]-N-[3-(2-hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		metil {3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]frenil}acetato EJEMPLO 30	HRMS calculado para C₁₉H₁₈Cl₂N₄O₂ Teo: 405.0885 Encontrado: 405.0869 TA: 2.84 min. PF: 142°

EJEMPLO 63

Ácido 3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoico

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Se agitó una mezcla de etil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino] benzoato (Ejemplo 20) (0.06 g, 0.138 mmoles) y una solución de 1N NaOH (2 mL, 2 mmoles) en etanol (5 mL) a 40°C por 4 horas. El solvente se evaporó y el residuo se acidificó con una solución de 1N HCl. El precipitado formado se filtró y secó. El compuesto del

título se obtuvo como un sólido blanco (53 mg, 96%). HRMS calculado para C₁₈H₁₄Cl₂N₄O₅ (M+H)⁺: 405.0521, encontró: 405.0520, TA: 2.23 min. PF: 267.6□

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 63:

CUADRO 16

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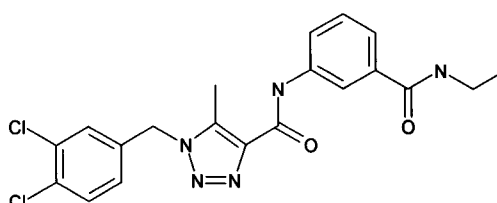
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Compuesto	Estructura	De	Datos físicos
Ejemplo 64 Ácido 3-(((1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-4-(metiloxi)benzoico		metil 3-(((1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino)-4-(metiloxi)benzoato EJEMPLO 25	HRMS calculado para C ₁₉ H ₁₆ Cl ₂ N ₄ O ₄ Teo: 435.0627 Encontrado: 435.0630 TA: 2.41 min PF: 243.9□
Ejemplo 65 Ácido 5-(((5-Metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il)carbonil)amino)-1,3-benceno dicarboxílico		dimetil 5-(((5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il)carbonil)amino)-1,3-bencen dicarboxilato (Intermediario 15)	HRMS calculado para C ₁₉ H ₁₆ N ₄ O ₅ Teo: 381.1199 Encontrado: 381.1231 TA: 1.59 min PF: 307.2□
Ejemplo 66 Ácido 4-(((1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino)benzoico		etil 4-(((1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino)benzoato EJEMPLO 48	HRMS calculado para C ₁₈ H ₁₄ Cl ₂ N ₄ O ₃ Teo: 405.0521 Encontrado: 405.0531 TA: 2.33 min MP>260°C

205

EJEMPLO 67**1-[(3,4-Diclorofenil)metil]-N-{3-[(etilamino)carbonil]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida**

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Se agitó una mezcla de ácido 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]benzoico (Ejemplo 63) (0.143 g, 0.35
10 mmoles), etilamina en THF, 2M de solución (1.75 mL, 0.35 mmoles), HATU (0.199 g, 0.52 mmoles) y DIPEA (0.09 mL, 0.52 mmoles) en DMF a 40°C por 1 semana. El solvente se evaporó y el residuo se lavó con agua y se extrajo con DCM. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El compuesto del título se obtuvo después de la recristalización de acetonitrilo
15 como un sólido blanco (49 mg, 32%). HRMS calculado para C₂₀H₁₉Cl₂N₅O₂ (M+H)⁺ 432.0994, encontró: 432.0957, TA: 2.82 min. PF: 192.2□

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 67:

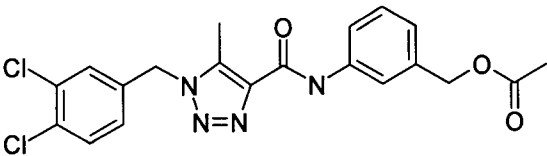
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CUADRO 17

Compuesto	Estructura	De	Datos físicos
Ejemplo 68 1-[(3,4-Diclorofenil)metil]-N-(3-[(2-hidroxietil)amino]carbonil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoico EJEMPLO 63 Y 2-aminoetanol	HRMS calculado para C ₂₀ H ₁₉ Cl ₂ N ₅ O ³ Teo: 448.0943 Encontrado: 448.0940 TA: 2.57 min. PF: 190.7°
Ejemplo 69 1-[(3,4-Diclorofenil)metil]-5-metil-N-[5-[(metilamino)carbonil]-2-(metiloxi)fenil]-1H-1,2,3-triazol-4-carboxamida		Ácido 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-4-(metiloxi)benzoico (Ejemplo 64) y metilamina	HRMS calculado para C ₂₀ H ₁₉ Cl ₂ N ₅ O ³ Teo: 448.0943 Encontrado: 448.0935 TA: 2.87 min. PF: 222.2°

EJEMPLO 70

{3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]fenil}metil acetato



A una solución de 1-[(3,4-diclorofenil)metil]-N-[3-(hidroximeto)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida (Ejemplo 24) (0.1 g, 0.25 mmoles) en una mezcla de DCM/THF se agregaron NEt₃ (75 µL, 2 eq) y

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cloruro de acetilo (25 µL, 1.2 eq). La reacción se agitó a temperatura ambiente durante 2 horas. Se añadió agua y el producto se extrajo con éter, se secó sobre sulfato de sodio y se evaporó al vacío. El compuesto de título se obtuvo como un sólido blanco después de la recristalización de éter de isopropilo (un par de gotas de DCM) (60 mg, 54.5%). HRMS calculado para C₂₀H₁₈Cl₂N₄O₃ (M+H)⁺ 433.0834, encontró: 433.0812, TA: 3.14 min. PF: >70°C (pegajosa).

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió para el Ejemplo 70:

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CUADRO 18

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Compuesto	Estructura	De	Datos físicos
Ejemplo 71 {3-[(1-[(3,5-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]fenil}metil acetato		1-[(3,5-diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida (Ejemplo 40)	HRMS calculado para C ₂₀ H ₁₈ Cl ₂ N ₄ O ₃ Teo: 433.0834 Encontrado: 433.0801 TA: 3.24 min. PF: 124°C
Ejemplo 72 {3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]fenil}metil benzoato		1-[(3,4-diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida (Ejemplo 24) y cloruro de benzoilo	HRMS calculado para C ₂₅ H ₂₀ Cl ₂ N ₄ O ₃ Teo: 495.0991 Encontrado: 495.0982 TA: 3.58 min. PF: 140°C

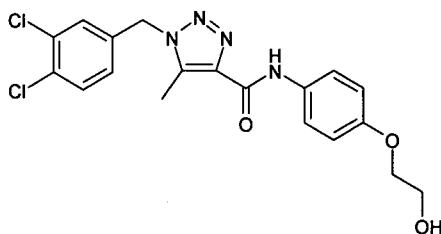
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Ejemplo 73		1-[(3,5-diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida (Ejemplo 40) y cloruro de benzoilo	HRMS calculado para $C_{25}H_{20}Cl_2N_4O_3$ Teo: 495.0991 Encontrado: 495.1003 TA: 3.71 min. PF: 85-95°C
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EJEMPLO 74

1-[(3,4-Diclorofenil)metil]-N-{4-[(2-hidroxietil)oxi]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida,

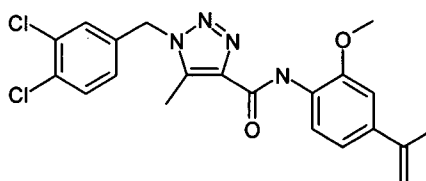
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A una solución de 1-[(3,4-diclorofenil)metil]-5-metil-N-(4-{[2-(tetrahidro-2H-piran-2-iloxi)etil]oxi}fenil)-1H-1,2,3-triazol-4-carboxamida crudo (Intermediario 19) en metanol se añadió una solución saturada de HCl en etil acetato. La reacción se agitó a 60°C durante 18 horas. Después de la evaporación, se obtuvo el compuesto del título como una crema sólida después de la recristalización a partir de metanol (0.23 g, 54% del intermediario 6). HRMS calculado para $C_{19}H_{18}Cl_2N_4O_3$ $(M+H)^+$ 421.0834, encontrado: 421.0837, TA: 2.76 min. PF: 140°C

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EJEMPLO 75**1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1-metiletenil)-2-(metiloxi)fenil]-1H-****1,2,3-triazol-4-carboxamida,**

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A una solución de metil 4-[[1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-3-(metiloxi)benzoato (ejemplo 17) (0.2 g, 0.45 mmoles) en THF (30 ml) se le agrogó una solución a 1M de bromuro de metil-
10 magnesio en THF (5 eq). Se agitó la reacción a temperatura ambiente durante 2 horas y se calentó a 60°C durante 2 horas. Después de enfriar, se agregó agua seguido por una solución de HCl a 1N y se extrajo el compuesto con éter, se secó sobre sulfato de sodio y se evaporó. Después de purificación por cromatografía de columna instantánea eluyendo con DCM y DCM/MeOH 92/8,
15 el compuesto del título se obtuvo como un sólido blanco (0.02 g, 10%). HRMS calculado para $C_{21}H_{20}Cl_2N_4O_2$ (M+H)⁺ 431.1042, encontró: 431.1028, TA: 3.69 min. PF: 170□

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 75:

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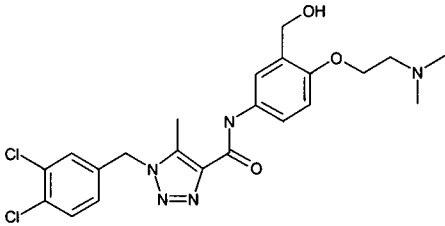
CUADRO 19

Compuesto	Estructura	De	Datos físicos
Ejemplo 76 1-[(3,4-Diclorofenil)metil]-N-[3-(1-hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		etil 3-[[{1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]benzoato EJEMPLO 20	HRMS calculado para C ₂₀ H ₂₀ Cl ₂ N ₄ O ² Teo: 417.0885 Encontrado: 417.0886 TA: 2.95 min. PF: 58°

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EJEMPLO 77

1-[(3,4-Diclorofenil)metil]-N-[4-{[2-(dimetilamino)etil]oxi}-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida



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A una solución de 1-[(3,4-diclorofenil)metil]-N-[4-hidroximetil-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida (Ejemplo 26) (0.1 g, 0.245 mmol) en DMF (10 ml) se le agregó carbonato de potasio (0.07 g, 2 eq) y (clorhidrato de 2-cloroetil)dimetilamina (0.07 g, 2 eq). La reacción se calentó a 40° durante 3 días. Después de la evaporación, se diluyó el residuo con DCM, se lavó con agua y se secó sobre sulfato de sodio. Después de purificación mediante cromatografía instantánea eluyendo con DCM/MeOH

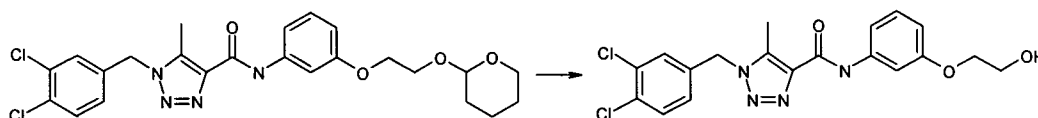
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(90/10) y recristalización de metanol, el compuesto del título se obtuvo como un sólido blanco (18 mg, 16%). HRMS calculado para $C_{22}H_{25}Cl_2N_5O_3$ ($M+H$)⁺ 478.1413, encontró: 478.1435, TA: 2.47 min. PF: 163.1□

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EJEMPLO 78

1-[(3,4-Diclorofenil)metil]-N-{3-[(2-hidroxietil)oxi]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida,



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A una solución de 1-[(3,4-diclorofenil)metil]-N-(3-hidroxifenil)-5-metil-1H-1,2,3-triazol-4-carboxamida (Ejemplo 31) (0.1 g, 0.29 mmol) en acetonitrilo (10 ml) y un par de gotas de DMF se les agregó 2-[(2-bromoetil)oxi]tetrahidro-2H-pirano (0.09 μ l, 2 eq) y carbonato de potasio (0.08 g, 2 eq). La reacción se calentó a 40□ durante 1 semana. Después de la evaporación, se diluyó el residuo con DCM, se lavó con agua y se secó sobre sulfato de sodio. Después de la purificación por cromatografía instantánea eluyendo con DCM/MeOH, 98/2, se disolvió el compuesto crudo en MeOH y se agregaron algunas gotas de una solución concentrada de HCl en AcOEt y se agitó la solución a temperatura ambiente durante 3 horas. Después de la evaporación, se recristalizó el compuesto (dos veces) a partir de metanol y se lavó con una mezcla de éter y pentano. El compuesto del título se obtuvo como un sólido verde (45 mg, 36%). HRMS calculado para $C_{19}H_{18}Cl_2N_4O_3$

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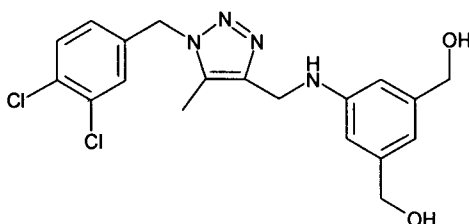
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$(M+H)^+$ 421.0834, encontró: 421.0804, TA: 2.87 min. PF: 144.9□

EJEMPLO 79

5-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)metil)amino]benceno-1,3-diil}dimetanol

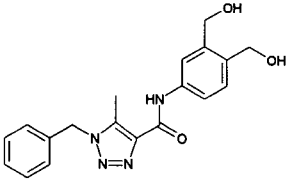
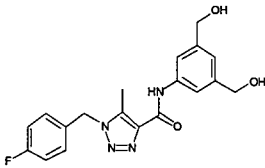
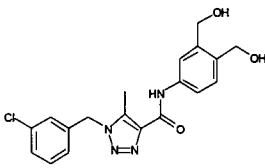
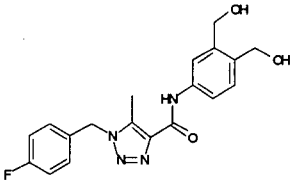


Se obtuvo este compuesto como producto secundario de la reducción de 5-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-bencendicarboxilato de dimetilo (Intermediario 14) en la preparación de N-[3,5-bis(hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida (ejemplo 52). Se obtuvo como un sólido blanco (5%) después de la recristalización de acetonitrilo. HRMS calculado para $C_{19}H_{20}Cl_2N_4O_2$ $(M+H)^+$ 407.1042, encontró: 407.1022, TA: 2.40 min. PF: 120□

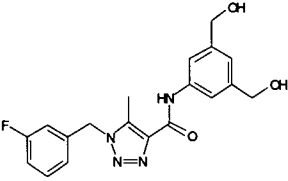
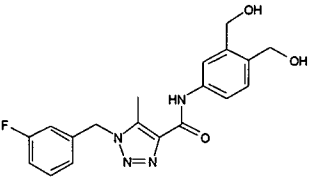
Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 49:

213

CUADRO 20

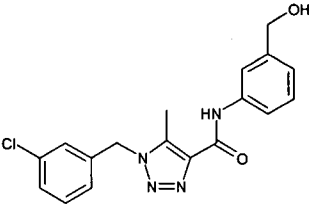
Compuesto	Estructura	De	Datos físicos
Ejemplo 80 N-[3,4-bis(Hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida		dimetil 4-(((5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il)carbonil)amino)-1,2-bencen dicarboxilato (Intermediario 20)	HRMS calculado para C ₁₉ H ₂₀ N ₄ O ₃ Teo: 353.1613 Encontrado: 353.1593 TA: 2.23 min. PF: 171.4□
Ejemplo 81 N-[3,5-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		dimetil 5-(((1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino)-1,3-bencen dicarboxilato (Intermediario 21)	HRMS calculado para C ₁₉ H ₁₉ FN ₄ O ₃ Teo: 371.1519 Encontrado: 371.1537 TA: 2.22 min. PF: 180.3□
Ejemplo 82 N-[3,4-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		dimetil 4-(((1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino)-1,2-bencen dicarboxilato (Intermediario 22)	HRMS calculado para C ₁₉ H ₁₉ ClN ₄ O ₃ Teo: 387.1224 Encontrado: 387.1223 TA: 2.41 min. PF: 157□
Ejemplo 83 N-[3,4-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		dimetil 4-(((1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino)-1,2-bencen dicarboxilato (Intermediario 23)	HRMS calculado para C ₁₉ H ₁₉ FN ₄ O ₃ Teo: 371.1519 Encontrado: 371.1544 TA: 2.29 min. PF: 175.5□

264

Ejemplo 84 N-[3,5-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		dimetil 5-[(1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-bencen dicarboxilato (Intermediario 27)	HRMS calculado para C₁₉H₁₉FN₄O₃ Teo: 369.1363 Encontrado: 369.1342 TA: 2.20 min. PF: 173.1□
Ejemplo 85 N-[3,4-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida		dimetil 5-[(1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-bencen dicarboxilato (Intermediario 28)	HRMS calculado para C₁₉H₁₉FN₄O₃ Teo: 371.1519 Encontrado: 371.1533 TA: 2.15 min. PF: 157.2□

Los siguientes compuestos se prepararon de igual manera por medio de un método análogo al que se describió en el Ejemplo 1:

CUADRO 21

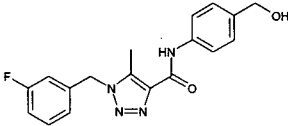
Compuesto	Estructura	De	Datos físicos
Ejemplo 86 1-[(3-clorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		Acido 1-[(3-Clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 13) y (3-aminofenil) metanol	HRMS calculado para C₁₈H₁₇ClN₄O₂ Teo: 355.0962 Encontrado: 355.0927 TA: 2.64 min PF: 151.9□

7/5

Compuesto	Estructura	De	Datos físicos
Ejemplo 87 1-[(4-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y (3-aminofenil) metanol	HRMS calculado para $C_{18}H_{17}FN_4O_2$ Teo: 339.1257 Encontrado: 339.1264 TA: 2.67 min PF: 142.1□
Ejemplo 88 1-[(3-clorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		Acido 1-[(3-Clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 13) y (4-aminofenil) metanol	HRMS calculado para $C_{18}H_{17}ClN_4O_2$ Teo: 357.1118 Encontrado: 357.1109 TA: 2.74 min PF: 136.2□
Ejemplo 89 1-[(3-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(3-Fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 26) y (3-aminofenil) metanol	HRMS calculado para $C_{18}H_{17}FN_4O_2$ (M-H)⁺ Teo: 339.1257 Encontrado: 339.1272 TA: 2.64 min PF: 124.7□
Ejemplo 90 1-[(4-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico y (4-aminofenil) metanol	HRMS calculado para $C_{18}H_{17}FN_4O_2$ Teo: 341.1414 Encontrado: 341.1434 TA: 2.61 min PF: 145.6□

76

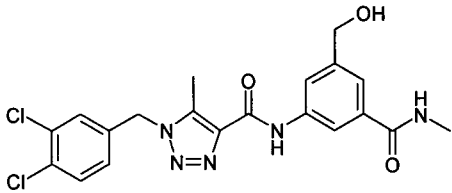
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Ejemplo 91 1-[(3-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida		ácido 1-[(3-Fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxílico (Intermediario 26) y (4-aminofenil) metanol	HRMS calculado para C ₁₈ H ₁₇ FN ₄ O ₂ Teo: 341.1414 Encontrado: 341.1427 TA: 2.57 min PF: 134.3°
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EJEMPLO 92

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1-[(3,4-diclorofenil)metil]-N-{3-(hidroximetil)-5-[(metilamino)carbonil]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida



A una solución de metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-5-[(metilamino)carbonil]benzoato (Intermedio 31) (0.206 g, 1.3 mmoles) en THF (5 mL), se agregó 1M de solución de LiAlH₄ en THF (0.65 µL, 1.5 eq). La reacción se agitó a temperatura ambiente durante una noche. Se añadió agua y el producto se extrajo con AcOEt, se secó sobre sulfato de sodio y se evaporó al vacío. Después de trituración de metanol caliente, el compuesto del título se obtuvo como un sólido blanco (0.03 g, 15.8%). HRMS calculado para C₂₀H₁₉Cl₂N₅O₃ (M+H)⁺ 448.0943, encontró: 448.0910, TA: 2.66 min. PF: 223-225°C.

Los siguientes compuestos se prepararon de manera similar por

2A

medio de un método análogo al que se describió en el Ejemplo 49:

CUADRO 22

	Compuesto	Estructura	De	Datos físicos
5	Ejemplo 93		Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]amino)carbonil] benzoato (Intermediario 34)	HRMS calculado para C ₁₈ H ₁₆ Cl ₂ N ₄ O ² Teo: 391.0728 Encontrado: 391.0740 TA: 2.47 min. PF: 160°
10	N-{1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}-4-(hidroximetil) benzamida			

Ensayo biológico

Los compuestos de la presente invención se pueden analizar *in vitro* en cuanto a actividad SCD usando un ensayo basado en la producción de [³H]H₂O, el cual se libera durante la generación catalizada con enzimas del producto acil-CoA monoinsaturado. Se realiza el ensayo en placas de filtración de 96 pozos. El sustrato titulado que se usa en el ensayo es la [9,10-³H]-estearoil-coenzima A. Después de la incubación durante 6 minutos de microsomas de rata que contenían SCD (2 µg de proteína) y sustrato (1 µM), se absorbe la especie marcada de ácido graso y acil-CoA y los microsomas con carbón vegetal y se separa del [³H]H₂O por centrifugación. La formación de [³H]H₂O se usa como medida de la actividad de SCD. Se preincuban compuestos a concentraciones a partir de 10 µM a 0.1 nM o vehículo (DMSO)

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durante 5 minutos con los microsomas antes de la adición del sustrato. Se hacen coincidir las respuestas de concentración con curvas sigmoidales para obtener valores de IC₅₀.

Se encontró que todos los compuestos sintéticos ejemplificativos 1-93 sometidos a prueba mediante el ensayo *in vitro* descrito anteriormente en cuanto a la actividad de SCD exhibían un valor medio de pIC₅₀ mayor a 5.5.

Se encontró que los compuestos siguientes se prepararon y cuando fueron sometidos a prueba mediante el ensayo *in vitro* descrito anteriormente en cuanto a la actividad de SCD exhibían un valor medio de pIC₅₀ de menos de 5.

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Nombre	Estructura
1-[(4-Bifenililmetil)-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida	
N-[3,4-Bis(metiloxi)fenil]-5-metil-1-{[4-(1-metiletil)fenil]metil}-1H-1,2,3-triazol-4-carboxamida	
Metil 5-[(1-{[3,4-diclorofenil]metil}-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-2-(metiloxi)benzoato	

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Dimetil 5-([5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il]carbonil)amino)-1,3-bencendicarboxilato	
Dimetil 5-([1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-1,3-bencendicarboxilato	
Ácido 5-([1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-1,3-bencendicarboxílico	
Metil 3-([1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-2-metilbenzoato,	
Dimetil 5-([1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-1,3-bencendicarboxilato	
5-([1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino]-N,N'-dimetil-1,3-bencendicarboxamida	

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Dimetil 4-([5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il]carbonil)amino)-1,2-bencendicarboxilato	
Dimetil 5-([1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]carbonil)amino)-1,3-bencendicarboxilato	
1-[(3,4-Diclorofenil)metil]-5-metil-N-{2-metil-3-[(metilamino)carbonil]fenil}-1H-1,2,3-triazol-4-carboxamida	

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Se encontró que los compuestos siguientes se prepararon y cuando fueron sometidos a prueba mediante el ensayo *in vitro* descrito anteriormente en cuanto a la actividad de SCD exhibían un valor medio de pIC_{50} de entre 5 y 5.5.

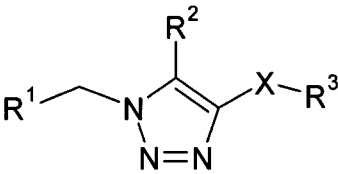
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Nombre	Estructura
1-[(4-Fluorofenil)metil]-5-metil-N-(5,6,7,8-tetrahidro-2-naftalenil)-1H-1,2,3-triazol-4-carboxamida	

NOVEDAD DE LA INVENCION

REIVINDICACIONES

5 1.- Un compuesto de fórmula (I):

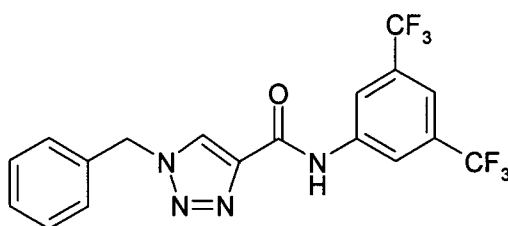


10 (I)

en donde: X representa -CONH-, -NHCO- o -CH₂NH-; R¹ representa: arilo de C₆₋₁₀ opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: (a) alquilo de C₁₋₆, -OCH₃, haloalquilo de C₁₋₆, haloalquilo de OC₁₋₆, cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno; (b) fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: halógeno; R² representa hidrógeno o alquilo de C₁₋₆; R³ representa: arilo de C₆₋₁₀ opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: (a) alquilo de C₁₋₆, alquenilo de C₁₋₆, alcoxi de C₁₋₆, -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, alquilo C₀₋₆OH, -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, haloalquilo de C₁₋₆, haloalquilo de OC₁₋₆, cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno; (b) heteroarilo de C₅; R⁴ representa arilo de C₆₋₁₀; R⁵ representa -H o alquilo de C₁₋₆; R⁶ representa -H o

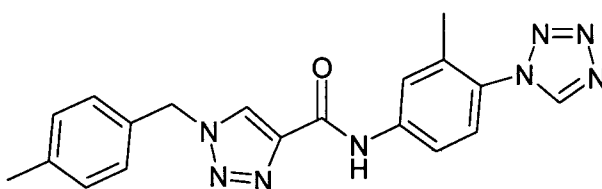
alquilo de C_{1-3} o alquilo $C_{1-3}OH$; R^7 representa -H o alquilo de C_{1-3} ; R^8 representa -H o alquilo de C_{1-3} ; R^9 representa -H o alquilo de C_{1-3} ; m representa 1-3; n representa 0-3; p representa 0-3; y q representa 1-3; o una sal farmacéuticamente aceptable del mismo; con la condición de que el

5 compuesto de fórmula (I) no sea N-[3,5-bis(trifluorometil)fenil]-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida,



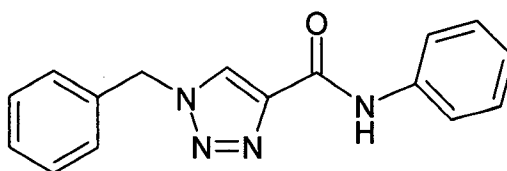
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N-[2-(5-metil-2-furanil)fenil]-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxamida,



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o, N-fenil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida



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2.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado además porque X representa -CONH- o -CH₂NH-.

3.- El compuesto de fórmula (I) o la sal farmacéuticamente

23

aceptable del mismo de conformidad con la reivindicación 1 o la reivindicación 2, caracterizado además porque R^1 representa fenilo opcionalmente sustituido por uno, dos o tres grupos independientemente seleccionados entre: (a) alquilo de C_{1-6} , $-OCH_3$, haloalquilo de C_{1-6} , haloalquilo de OC_{1-6} , cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno; (b) fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: halógeno.

4.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque R^2 representa hidrógeno o alquilo de C_{1-3} .

10 5.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^3 representa fenilo opcionalmente sustituido por uno, dos o tres grupos independientemente seleccionados entre: (a) alquilo de C_{1-6} , alqueno de C_{1-6} , alcoxi de C_{1-6} , $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$, $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}alkylOH$, haloalquilo de C_{1-6} , haloalquilo de OC_{1-6} , cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno; (b) heteroarilo de C_5 .

20 6.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^3 representa fenilo opcionalmente sustituido por: (i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$ o $-C(=O)NHR^6$ y/o, (ii) uno, dos o tres grupos seleccionados

independientemente de: (a) alquilo de C_{1-6} , alquenilo de C_{1-6} , alcoxi de C_{1-6} , $O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo de C_{1-6} , haloalquilo de OC_{1-6} , cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno; (b)

5 heteroarilo de C_5 .

7.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque se selecciona entre: N-[3,4-bis(Metiloxi)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-bis(Metiloxi)fenil]-1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Bromofenil)metil]-5-metil-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Fluorofenil)metil]-5-metil-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Fluorofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Bromofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 5-Metil-1-(fenilmetil)-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida, 1-[(2'-Cloro-4-bifenilil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxamida, 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-[[4-(1-metiletil)fenil]metil]-1H-1,2,3-triazol-4-carboxamida, N-[3,4-Bis(metiloxi)fenil]-5-metil-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxamida, 1-(2-Bifenililmetil)-N-[3,4-bis(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-Bis(metiloxi)fenil]-1-[(4-fluorofenil)metil]-

- 1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1,3-oxazol-2-il)fenil]-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-3-
- 5 (metiloxi)benzoato, 1-[(3,4-Diclorofenil)metil]-5-metil-N-{3-[(metilamino)carbonil]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-{4-[(metilamino)carbonil]fenil}-1H-1,2,3-triazol-4-carboxamida, Etil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]benzoato, N-[3-(acetilamino)fenil]-1-[(3,4-diclorofenil)metil]-5-
- 10 metil-1H-1,2,3-triazol-4-carboxamida, N-[4-(acetilamino)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-
- 15 1,2,3-triazol-4-il}carbonil)amino]-4-(metiloxi)benzoato, 1-[(3,4-Diclorofenil)metil]-N-[4-hidroxi-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Etil {4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}acetato, Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-(metiloxi)benzoato, Metil 5-[(1-[(3,4-
- 20 diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-hidroxibenzoato, Metil {3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}acetato, 1-[(3,4-Diclorofenil)metil]-N-(3-hidroxifenil)-5-metil-1H-1,2,3-triazol-4-carboxamida, Metil 5-[(1-[(3,4-diclorofenil)metil]-5-

metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-fluorobenzoato, N-[5-
 (Aminocarbonil)-2-(metiloxo)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-
 triazol-4-carboxamida, Metil 4-cloro-3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-
 1,2,3-triazol-4-il}carbonil)amino]benzoato, Metil [3-[(1-[(3,4-diclorofenil)metil]-
 5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-4-(metiloxo)fenil]acetato, Metil 3-
 5 5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-4-(metiloxo)fenil]acetato, Metil 3-
 [(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-4-
 fluorobenzoato, N-[3-(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-
 carboxamida, N-[4-(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-
 carboxamida, N-[3-(hidroximetil)-2-metilfenil]-5-metil-1-(fenilmetil)-1H-1,2,3-
 10 triazol-4-carboxamida, 1-[(3,5-Diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-
 metil-1H-1,2,3-triazol-4-carboxamida, Metil 3-[(1-[(3,5-diclorofenil)metil]-5-
 metil-1H-1,2,3-triazol-4-il}carbonil)amino]-4-(metiloxi)benzoato, 1-[(3,5-
 Diclorofenil)metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-1H-1,2,3-triazol-4-
 carboxamida, N-[3-[(Acetilamino)metil]fenil]-1-[(3,4-diclorofenil)metil]-5-metil-
 15 1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(1-
 hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[4-cloro-3-
 (Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
 carboxamida, Dimetil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
 il}carbonil)amino]-1,2-bencendicarboxilato, Metil 5-[(1-[(3,5-diclorofenil)metil]-
 20 5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-fluorobenzoato, Etil 4-[(1-[(3,4-
 diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]benzoato, 1-[(3,4-
 Diclorofenil)metil]-N-[4-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-
 4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-(2-hidroxietil)fenil]-5-metil-1H-

- 1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[5-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[5-(2-hidroxietil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[2-fluoro-5-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[2-cloro-5-(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,5-Diclorofenil)metil]-N-[5-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,5-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(2-hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Ácido 3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoico, Ácido 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-4-(metiloxi)benzoico, ácido 5-[(5-Metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il)carbonil)amino]-1,3-bencendicarboxílico, Ácido 4-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoico, 1-[(3,4-Diclorofenil)metil]-N-{3-[(etilamino)carbonil]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-

Diclorofenil)metil]-N-(3-[(2-hidroxietil)amino]carbonil}fenil)-5-metil-1H-1,2,3-
 triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-[5-
 [(metilamino)carbonil]-2-(metiloxi)fenil]-1H-1,2,3-triazol-4-carboxamida, {3-[(1-
 [(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}metil
 5 acetato, {3-[(1-[(3,5-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
 il}carbonil)amino]fenil}metil acetato, {3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-
 1,2,3-triazol-4-il}carbonil)amino]fenil}metil benzoato, {3-[(1-[(3,5-
 Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}metil
 benzoato, 1-[(3,4-Diclorofenil)metil]-N-[4-[(2-hidroxietil)oxi]fenil]-5-metil-1H-
 10 1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1-
 metiletenil)-2-(metiloxi)fenil]-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-
 Diclorofenil)metil]-N-[3-(1-hidroxi-1-metiletil)fenil]-5-metil-1H-1,2,3-triazol-4-
 carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-[[2-(dimetilamino)etil]oxi]-3-
 (hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-
 15 Diclorofenil)metil]-N-[3-[(2-hidroxietil)oxi]fenil]-5-metil-1H-1,2,3-triazol-4-
 carboxamida, y {5-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
 il}metil)amino]benceno-1,3-diil}dimetanol, o una sal farmacéuticamente
 aceptable del mismo.

8.- El compuesto de fórmula (I) de conformidad con la
 20 reivindicación 1, caracterizado además porque se selecciona entre: N-[3,4-
 bis(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida, N-
 [3,5-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
 carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-

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1,2,3-triazol-4-carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-clorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(4-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-clorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(4-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-diclorofenil)metil]-N-[3-(hidroximetil)-5-[(metilamino)carbonil]fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, y N-[1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]-4-(hidroximetil)benzamida o una sal farmacéuticamente aceptable del mismo.

9.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque es N-[3,5-bis(hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida o una sal farmacéuticamente aceptable del mismo.

10.- Una composición farmacéutica que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en cualquiera de las reivindicaciones 1 a 9, por lo menos junto con un portador y/o excipiente.

11.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa en terapia.

5 12.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en cualquiera de las reivindicaciones 1 a 9, en la elaboración de un medicamento para tratar y/o prevenir una enfermedad o afección susceptible de mejoría por medio de un inhibidor de SCD.

10 13.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la reivindicación 12, en la elaboración de un medicamento para tratar y/o prevenir enfermedades o afecciones causadas por o asociadas con un perfil anormal de lípidos en el plasma incluyendo dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, 15 hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, aterosclerosis, obesidad, diabetes de tipo I, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia y síndrome metabólico; enfermedad vascular periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones 20 vasculares de la diabetes, trombosis, esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras enfermedades relacionadas con la acumulación de lípidos en el hígado; eczema, acné, psoriasis, envejecimiento de la piel, formación o prevención de cicatrices queloidales, y enfermedades

relacionadas con la producción o las secreciones de las membranas mucosas; cáncer, neoplasia, malignidad, metástasis, tumores (benignos o malignos), carcinogenesis, hepatomas y similares; deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloida cerebral (CAA) o
5 demencia asociada con síndrome de Down (DS) y otras enfermedades neurodegenerativas caracterizadas por la formación o acumulación de placas amiloidales que comprenden A β 42.

14.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la
10 reivindicación 12, en la elaboración de un medicamento para tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no alcohólica (NASH).

15 15.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la reivindicación 12 en la elaboración de un medicamento para tratar y/o prevenir acné.

20 16.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa para tratar y/o prevenir una enfermedad o afección susceptible de mejoría por medio de un inhibidor de SCD.

17.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 16, caracterizado además porque se usa para tratar y/o prevenir enfermedades o afecciones causadas por o asociadas con un perfil anormal de lípidos en el plasma

5 incluyendo dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, aterosclerosis, obesidad, diabetes de tipo I, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia y síndrome metabólico; enfermedad vascular

10 periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de la diabetes, trombosis, esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras enfermedades relacionadas con la acumulación de lípidos en el hígado; eczema, acné, psoriasis, envejecimiento de la piel, formación o prevención de cicatrices queloidales, y

15 enfermedades relacionadas con la producción o las secreciones de las membranas mucosas; cáncer, neoplasia, malignidad, metástasis, tumores (benignos o malignos), carcinogenesis, hepatomas y similares; deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloida cerebral (CAA) o demencia asociada con síndrome de Down (DS) y otras

20 enfermedades neurodegenerativas caracterizadas por la formación o acumulación de placas amiloidales que comprenden A β 42.

18.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 16, caracterizado

además porque se usa en la elaboración de un medicamento para tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no
5 alcohólica (NASH).

19.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 16, caracterizado además porque se usa para tratar y/o prevenir acné.

20.- Un método de tratar y/o prevenir una enfermedad o afección
10 susceptible de mejoría por medio de un SCD, que comprende administrar a un sujeto una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en cualquiera de las reivindicaciones 1 a 9.

21.- Un método de tratar y/o prevenir enfermedades o
15 afecciones causadas por o asociadas con un perfil anormal de lípidos en el plasma incluyendo dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, aterosclerosis, obesidad, diabetes de
20 tipo I, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia y síndrome metabólico; enfermedad vascular periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de la diabetes, trombosis, esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras



enfermedades relacionadas con la acumulación de lípidos en el hígado; eczema, acné, psoriasis, envejecimiento de la piel, formación o prevención de cicatrices queloidales, y enfermedades relacionadas con la producción o las secreciones de las membranas mucosas; cáncer, neoplasia, malignidad, metástasis, tumores (benignos o malignos), carcinogenesis, hepatomas y similares; deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloida cerebral (CAA) o demencia asociada con síndrome de Down (DS) y otras enfermedades neurodegenerativas caracterizadas por la formación o acumulación de placas amiloidales que comprenden A β 42.

10 22.- Un método de tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no alcohólica (NASH), que comprende administrar a un sujeto una cantidad terapéuticamente efectiva de un
15 compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la reivindicación 20.

23.- Un método de tratar y/o prevenir acné, que comprende administrar a un sujeto una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo
20 como el que se reclama en la reivindicación 20.

24.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa en combinación con uno o más

agentes activos seleccionados entre un inhibidor de éster colesterílico transferasa (inhibidores de CETP), un inhibidor de HMG-CoA reductasa, una proteína microsomal de transferencia de triglicéridos, un activador de receptor activado mediante proliferador de peroxisoma (PPAR), un inhibidor de
5 resorción de ácidos biliares, un inhibidor de absorción de colesterol, un inhibidor de síntesis de colesterol, un fibrato, niacina, una resina de intercambio de iones, un antioxidante, un inhibidor de AcylCoA: colesterol aciltransferasa (ACAT inhibidor), un antagonista de canabinoide 1 y un secuestrante de ácidos biliares.

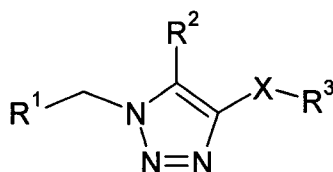
10 25.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa en combinación con uno o más agentes activos seleccionados entre un corticosteroide, un derivado de vitamina D3, un retinoide, un inmunomodulador, un antiandrógeno, un agente
15 queratolítico, un antimicrobiano, un quimioterapéutico de platino, un antimetabolito, hidroxurea, un taxano, un interruptor mitótico, una antraciclina, dactinomicina, un agente de alquilación y un inhibidor de colinesterasa.



RESUMEN DE LA INVENCION

La presente invención se refiere a compuestos de triazol
sustituídos de la fórmula (I):

5



(I)

y sales farmacéuticamente aceptables de los mismos, a composiciones
10 farmacéuticas que los contienen y a su uso en medicina; en particular, la
invención se refiere a compuestos para modular la actividad de SCD.

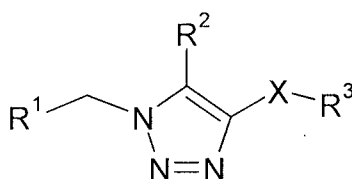
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NOVEDAD DE LA INVENCION

TRADUCCION REIVINDICACIONES IPRP

REIVINDICACIONES

5 1.- Un compuesto de fórmula (I):

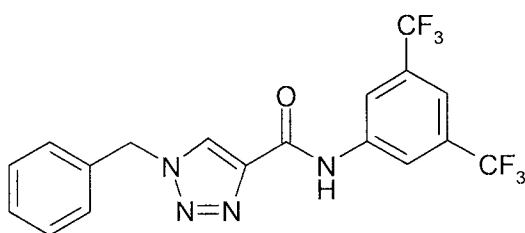


10 (I)

en donde: X representa -CONH-, -NHCO- o -CH₂NH-; R¹ representa: arilo de C₆₋₁₀ opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: (a) alquilo de C₁₋₆, -OCH₃, haloalquilo de C₁₋₆, haloalquilo de OC₁₋₆, cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno; (b) fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: halógeno; R² representa alquilo de C₁₋₆; R³ representa: arilo de C₆₋₁₀ opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: (a) alquilo de C₁₋₆, alquenilo de C₁₋₆, alcoxi de C₁₋₆, -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, alquilo C₀₋₆OH, -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, haloalquilo de C₁₋₆, haloalquilo de OC₁₋₆, cicloalquilo de C₃₋₆, cicloalquilo de OC₃₋₆ o halógeno; (b) oxazol; R⁴ representa arilo de C₆₋₁₀; R⁵ representa -H o alquilo de C₁₋₆; R⁶ representa -H o alquilo de

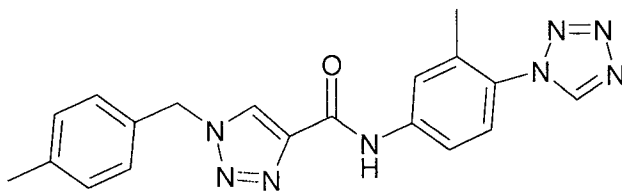
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C₁₋₃ o alquilo C₁₋₃OH; R⁷ representa -H o alquilo de C₁₋₃; R⁸ representa -H o alquilo de C₁₋₃; R⁹ representa -H o alquilo de C₁₋₃; m representa 1-3; n representa 0-3; p representa 0-3; y q representa 1-3; o una sal farmacéuticamente aceptable del mismo; con la condición de que el
 5 compuesto de fórmula (I) no sea N-[3,5-bis(trifluorometil)fenil]-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida,



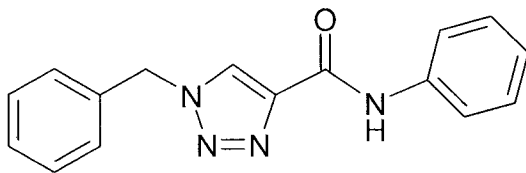
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N-[2-(5-metil-2-furanil)fenil]-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxamida,



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o, N-fenil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida



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2.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 1, caracterizado además porque X representa -CONH- o -CH₂NH-.

3.- El compuesto de fórmula (I) o la sal farmacéuticamente

aceptable del mismo de conformidad con la reivindicación 1 o la reivindicación 2, caracterizado además porque R^1 representa fenilo opcionalmente sustituido por uno, dos o tres grupos independientemente seleccionados entre: (a) alquilo de C_{1-6} , $-OCH_3$, haloalquilo de C_{1-6} , haloalquilo de OC_{1-6} , cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno; (b) fenilo opcionalmente sustituido por uno, dos o tres grupos seleccionados independientemente de: halógeno.

4.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque R^2 representa hidrógeno o alquilo de C_{1-3} .

10 5.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^3 representa fenilo opcionalmente sustituido por uno, dos o tres grupos independientemente seleccionados entre: (a) alquilo de C_{1-6} , alquenilo de C_{1-6} , alcoxi de C_{1-6} , $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$, $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}alkylOH$, haloalquilo de C_{1-6} , haloalquilo de OC_{1-6} , cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno; (b) oxazol.

20 6.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque R^3 representa fenilo opcionalmente sustituido por: (i) un grupo seleccionado independientemente de $-(CH_2)_nCO_2R^5$ o $-C(=O)NHR^6$ y/o, (ii) uno, dos o tres grupos seleccionados

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independientemente de: (a) alquilo de C_{1-6} , alquenilo de C_{1-6} , alcoxi de C_{1-6} , $O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, alquilo $C_{0-6}OH$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, alquilo $OC_{1-6}OH$, haloalquilo de C_{1-6} , haloalquilo de OC_{1-6} , cicloalquilo de C_{3-6} , cicloalquilo de OC_{3-6} o halógeno; (b) heteroarilo de C_5 .

7.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque se selecciona entre: N-[3,4-bis(Metiloxi)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-bis(Metiloxi)fenil]-1-[(4-bromofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Bromofenil)metil]-5-metil-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Fluorofenil)metil]-5-metil-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Fluorofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(4-Bromofenil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 5-Metil-1-(fenilmetil)-N-{4-[(fenilmetil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida, 1-[(2'-Cloro-4-bifenilil)metil]-5-metil-N-{4-[(3-metilbutil)oxi]fenil}-1H-1,2,3-triazol-4-carboxamida, 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxamida, 5-Metil-N-{4-[(3-metilbutil)oxi]fenil}-1-[[4-(1-metiletil)fenil]metil]-1H-1,2,3-triazol-4-carboxamida, N-[3,4-Bis(metiloxi)fenil]-5-metil-1-[(4-metilfenil)metil]-1H-1,2,3-triazol-4-carboxamida, 1-(2-Bifenililmetil)-N-[3,4-bis(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-Bis(metiloxi)fenil]-1-[(4-fluorofenil)metil]-

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1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1,3-oxazol-2-il)fenil]-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-3-

5 (metiloxi)benzoato, 1-[(3,4-Diclorofenil)metil]-5-metil-N-{3-[(metilamino)carbonil]fenil}-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-{4-[(metilamino)carbonil]fenil}-1H-1,2,3-triazol-4-carboxamida, Etil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]benzoato, N-[3-(acetilamino)fenil]-1-[(3,4-diclorofenil)metil]-5-

10 metil-1H-1,2,3-triazol-4-carboxamida, N-[4-(acetilamino)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Metil 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-

15 1,2,3-triazol-4-il}carbonil)amino]-4-(metiloxi)benzoato, 1-[(3,4-Diclorofenil)metil]-N-[4-hidroxi-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Etil {4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}acetato, Metil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-(metiloxi)benzoato, Metil 5-[(1-[(3,4-

20 diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-hidroxibenzoato, Metil {3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}acetato, 1-[(3,4-Diclorofenil)metil]-N-(3-hidroxifenil)-5-metil-1H-1,2,3-triazol-4-carboxamida, Metil 5-[(1-[(3,4-diclorofenil)metil]-5-

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metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-fluorobenzoato, N-[5-
(Aminocarbonil)-2-(metiloxo)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-
triazol-4-carboxamida, Metil 4-cloro-3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-
1,2,3-triazol-4-il}carbonil)amino]benzoato, Metil [3-[(1-[(3,4-diclorofenil)metil]-
5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-4-(metiloxo)fenil]acetato, Metil 3-
5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-4-
fluorobenzoato, N-[3-(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-
carboxamida, N-[4-(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-
carboxamida, N-[3-(hidroximetil)-2-metilfenil]-5-metil-1-(fenilmetil)-1H-1,2,3-
10 triazol-4-carboxamida, 1-[(3,5-Diclorofenil)metil]-N-[3-(hidroximetil)fenil]-5-
metil-1H-1,2,3-triazol-4-carboxamida, Metil 3-[(1-[(3,5-diclorofenil)metil]-5-
metil-1H-1,2,3-triazol-4-il}carbonil)amino]-4-(metiloxi)benzoato, 1-[(3,5-
Diclorofenil)metil]-N-[3-(hidroximetil)-2-metilfenil]-5-metil-1H-1,2,3-triazol-4-
carboxamida, N-[3-[(Acetilamino)metil]fenil]-1-[(3,4-diclorofenil)metil]-5-metil-
15 1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(1-
hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[4-cloro-3-
(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
carboxamida, Dimetil 4-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-
il}carbonil)amino]-1,2-bencendicarboxilato, Metil 5-[(1-[(3,5-diclorofenil)metil]-
20 5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]-2-fluorobenzoato, Etil 4-[(1-[(3,4-
diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]benzoato, 1-[(3,4-
Diclorofenil)metil]-N-[4-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-
4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-(2-hidroxietil)fenil]-5-metil-1H-

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1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[5-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[5-(2-hidroxietil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[2-fluoro-5-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[2-cloro-5-(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,5-Diclorofenil)metil]-N-[5-(hidroximetil)-2-(metiloxi)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,5-Diclorofenil)metil]-N-[4-fluoro-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(2-hidroxietil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, Ácido 3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoico, Ácido 3-[(1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]-4-(metiloxi)benzoico, ácido 5-([5-Metil-1-(fenilmetil)-1H-1,2,3-triazol-4-il)carbonil)amino)-1,3-bencendicarboxílico, Ácido 4-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il)carbonil)amino]benzoico, 1-[(3,4-Diclorofenil)metil]-N-[3-[(etilamino)carbonil]fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-

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Diclorofenil)metil]-N-(3-[(2-hidroxietil)amino]carbonil}fenil)-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-[5-[(metilamino)carbonil]-2-(metiloxi)fenil]-1H-1,2,3-triazol-4-carboxamida, {3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}metil acetato, {3-[(1-[(3,5-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}metil acetato, {3-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}metil benzoato, {3-[(1-[(3,5-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}carbonil)amino]fenil}metil benzoato, 1-[(3,4-Diclorofenil)metil]-N-{4-[(2-hidroxietil)oxi]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-5-metil-N-[4-(1-metiletenil)-2-(metiloxi)fenil]-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[3-(1-hidroxi-1-metiletil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-[4-{2-(dimetilamino)etil}oxi]-3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-Diclorofenil)metil]-N-{3-[(2-hidroxietil)oxi]fenil}-5-metil-1H-1,2,3-triazol-4-carboxamida, y {5-[(1-[(3,4-Diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il}metil)amino]benceno-1,3-diil}dimetanol, o una sal farmacéuticamente aceptable del mismo.

8.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque se selecciona entre: N-[3,4-bis(hidroximetil)fenil]-5-metil-1-(fenilmetil)-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(3-clorofenil)metil]-5-metil-1H-

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- 1,2,3-triazol-4-carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(4-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,5-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, N-[3,4-bis(Hidroximetil)fenil]-1-[(3-fluorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-clorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(4-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-clorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-fluorofenil)metil]-N-[3-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(4-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3-fluorofenil)metil]-N-[4-(hidroximetil)fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, 1-[(3,4-diclorofenil)metil]-N-[3-(hidroximetil)-5-[(metilamino)carbonil]fenil]-5-metil-1H-1,2,3-triazol-4-carboxamida, y N-[1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-il]-4-(hidroximetil)benzamida o una sal farmacéuticamente aceptable del mismo.

9.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque es N-[3,5-bis(hidroximetil)fenil]-1-[(3,4-diclorofenil)metil]-5-metil-1H-1,2,3-triazol-4-carboxamida o una sal farmacéuticamente aceptable del mismo.

10.- Una composición farmacéutica que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, como el que se reclama en cualquiera de las reivindicaciones 1 a 9, por lo menos junto con un portador y/o excipiente.

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11.- El compuesto de fórmula (I) o la sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa en terapia.

12.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en cualquiera de las reivindicaciones 1 a 9, en la elaboración de un medicamento para tratar y/o prevenir una enfermedad o afección susceptible de mejoría por medio de un inhibidor de SCD.

13.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la reivindicación 12, en la elaboración de un medicamento para tratar y/o prevenir enfermedades o afecciones causadas por o asociadas con un perfil anormal de lípidos en el plasma incluyendo dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, aterosclerosis, obesidad, diabetes de tipo I, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia y síndrome metabólico; enfermedad vascular periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de la diabetes, trombosis, esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras enfermedades relacionadas con la acumulación de lípidos en el hígado; eczema, acné, psoriasis, envejecimiento de la piel, formación o prevención de cicatrices queloidales, y enfermedades

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relacionadas con la producción o las secreciones de las membranas mucosas; cáncer, neoplasia, malignidad, metástasis, tumores (benignos o malignos), carcinogenesis, hepatomas y similares; deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloida cerebral (CAA) o
5 demencia asociada con síndrome de Down (DS) y otras enfermedades neurodegenerativas caracterizadas por la formación o acumulación de placas amiloidales que comprenden A β 42.

14.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la
10 reivindicación 12, en la elaboración de un medicamento para tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no alcohólica (NASH).

15 15.- El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la reivindicación 12 en la elaboración de un medicamento para tratar y/o prevenir acné.

20 16.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa para tratar y/o prevenir una enfermedad o afección susceptible de mejoría por medio de un inhibidor de SCD.

además porque se usa en la elaboración de un medicamento para tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no
5 alcohólica (NASH).

19.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 16, caracterizado además porque se usa para tratar y/o prevenir acné.

20.- Un método de tratar y/o prevenir una enfermedad o afección susceptible de mejoría por medio de un SCD, que comprende administrar a un sujeto una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en cualquiera de las reivindicaciones 1 a 9.

21.- Un método de tratar y/o prevenir enfermedades o
15 afecciones causadas por o asociadas con un perfil anormal de lípidos en el plasma incluyendo dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, aterosclerosis, obesidad, diabetes de
20 tipo I, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia y síndrome metabólico; enfermedad vascular periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de la diabetes, trombosis, esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras

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17.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 16, caracterizado además porque se usa para tratar y/o prevenir enfermedades o afecciones causadas por o asociadas con un perfil anormal de lípidos en el plasma

5 incluyendo dislipidemia, hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, angina, isquemia, isquemia cardíaca, accidente cerebrovascular, infarto de miocardio, aterosclerosis, obesidad, diabetes de tipo I, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia y síndrome metabólico; enfermedad vascular

10 periférica, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de la diabetes, trombosis, esteatosis hepática, esteatohepatitis no alcohólica (NASH) y otras enfermedades relacionadas con la acumulación de lípidos en el hígado; eczema, acné, psoriasis, envejecimiento de la piel, formación o prevención de cicatrices queloidales, y

15 enfermedades relacionadas con la producción o las secreciones de las membranas mucosas; cáncer, neoplasia, malignidad, metástasis, tumores (benignos o malignos), carcinogenesis, hepatomas y similares; deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloid cerebral (CAA) o demencia asociada con síndrome de Down (DS) y otras

20 enfermedades neurodegenerativas caracterizadas por la formación o acumulación de placas amiloidales que comprenden A β 42.

18.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con la reivindicación 16, caracterizado

enfermedades relacionadas con la acumulación de lípidos en el hígado; eczema, acné, psoriasis, envejecimiento de la piel, formación o prevención de cicatrices queloidales, y enfermedades relacionadas con la producción o las secreciones de las membranas mucosas; cáncer, neoplasia, malignidad, metástasis, tumores (benignos o malignos), carcinogenesis, hepatomas y similares; deterioro cognitivo leve (MCI), enfermedad de Alzheimer (AD), angiopatía amiloida cerebral (CAA) o demencia asociada con síndrome de Down (DS) y otras enfermedades neurodegenerativas caracterizadas por la formación o acumulación de placas amiloidales que comprenden A β 42.

10 22.- Un método de tratar y/o prevenir acné, psoriasis, envejecimiento de la piel, dislipidemia, hipertrigliceridemia, aterosclerosis, obesidad, diabetes de tipo II, resistencia a la insulina, hiperinsulinemia, esteatosis hepática y/o esteatohepatitis no alcohólica (NASH), que comprende administrar a un sujeto una cantidad terapéuticamente efectiva de un
15 compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como el que se reclama en la reivindicación 20.

23.- Un método de tratar y/o prevenir acné, que comprende administrar a un sujeto una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo
20 como el que se reclama en la reivindicación 20.

24.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa en combinación con uno o más

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agentes activos seleccionados entre un inhibidor de éster coleserílico transferasa (inhibidores de CETP), un inhibidor de HMG-CoA reductasa, una proteína microsomal de transferencia de triglicéridos, un activador de receptor activado mediante proliferador de peroxisoma (PPAR), un inhibidor de
5 resorción de ácidos biliares, un inhibidor de absorción de colesterol, un inhibidor de síntesis de colesterol, un fibrato, niacina, una resina de intercambio de iones, un antioxidante, un inhibidor de AcylCoA: colesterol aciltransferasa (ACAT inhibidor), un antagonista de canabinoide 1 y un secuestrante de ácidos biliares.

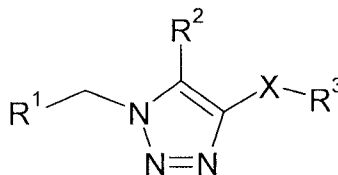
10 25.- El compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque se usa en combinación con uno o más agentes activos seleccionados entre un corticosteroide, un derivado de
15 vitamina D3, un retinoide, un inmunomodulador, un antiandrógeno, un agente queratolítico, un antimicrobiano, un quimioterapéutico de platino, un antimetabolito, hidroxurea, un taxano, un interruptor mitótico, una antraciclina, dactinomicina, un agente de alquilación y un inhibidor de colinesterasa.

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RESUMEN DE LA INVENCION

La presente invención se refiere a compuestos de triazol
sustituídos de la fórmula (I):

5



(I)

10 y sales farmacéuticamente aceptables de los mismos, a composiciones
farmacéuticas que los contienen y a su uso en medicina; en particular, la
invención se refiere a compuestos para modular la actividad de SCD.

15

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P10/476F

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

To:

GLAXOSMITHKLINE
Corporate Intellectual Property CN925.1
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing
(day/month/year)

02.10.2009

Applicant's or agent's file reference
DCG/PB62693

IMPORTANT NOTIFICATION

International application No.
PCT/EP2008/065104

International filing date (day/month/year)
07.11.2008

Priority date (day/month/year)
09.11.2007

Applicant
SMITHKLINE BEECHAM CORPORATION

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 inventions 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:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Authorized Officer

Gallego, Antonio

Tel. +49 89 2399-8102



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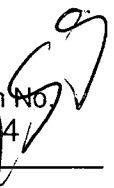
PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DCG/PB62693	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/EP2008/065104	International filing date (day/month/year) 07.11.2008	Priority date (day/month/year) 09.11.2007
International Patent Classification (IPC) or national classification and IPC INV. C07D249/04		
Applicant SMITHKLINE BEECHAM CORPORATION		
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 <u>4</u> 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 <u>11</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).		
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application		
Date of submission of the demand 2009-08-20	Date of completion of this report 02.10.2009	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Authorized officer Johnson, Claire Telephone No. +49 89 2399-5932	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No. 
PCT/EP2008/065104

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-74 as originally filed

Claims, Numbers

1-25 received on 21.08.2009 with letter of 20.08.2009

- ☐ 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*):
5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).
6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY

International application No.
PCT/EP2008/065104

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	<u>1-25</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-25</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-25</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. Reasoned statement

Novelty

The compounds having the registry numbers 950075-10-2, 949879-07-6 and 931967-53-2, cited in the search report as "X", do not fall within the scope of formula (I) because present R^2 cannot be H. The requirements of novelty are fulfilled.

Inventive step

The technical problem underlying the present claims is the provision of inhibitors of stearoyl-CoA desaturase (SCD). Document WO2005/011657 (hereafter known as D1) describes compounds with this activity. However, the compounds of D1 differ significantly from those of the present application, in particular lacking the present triazole ring attached to an aryl ring via a methylene group. No documents have been found which would have encouraged the skilled person, starting from the compounds of D1, to perform the extensive modifications necessary to arrive at the present compounds, in the expectation that the qualitative activity would be maintained. Those of the present compounds which have the alleged activity may therefore be regarded as inventive.

Industrial applicability

The present claims fulfil the requirements of industrial applicability. However, claims 20-23 relate to medical methods. The EPO does not recognise as patentable claims to the use of a compound in medical treatment, but allows claims to a product for use in a first or further medical treatment.

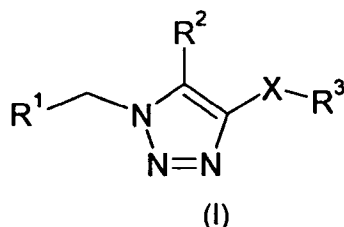
VIII. Certain observations

The provisos at the end of claim 1 are redundant as the excluded compounds have $R^2 = H$, which is not possible in the definition of formula (I).

Claim 7, dependent on claim 1, contains a compound (N-[3,4-Bis(methoxy)phenyl]-1-[(4-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxamide, 3rd compound on p. 4), which does not fall within the scope of claim 1 as R^2 is H.

Claims

1. A compound of formula (I):



wherein:

X represents -CONH-, -NHCO- or -CH₂NH-;

R¹ represents:

-C₆₋₁₀aryl optionally substituted by one, two or three groups independently selected from:

- (a) -C₁₋₆alkyl, -OCH₃, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen;
- (b) phenyl optionally substituted by one, two or three groups independently selected from: halogen;

R² represents -C₁₋₆alkyl;

R³ represents:

-C₆₋₁₀aryl optionally substituted by one, two or three groups independently selected from:

- (a) -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkoxy, -O(CH₂)_mR⁴, -(CH₂)_mOC(=O)R⁴, -(CH₂)_nCO₂R⁵, -(CH₂)_nOC(=O)R⁵, -C₀₋₆alkylOH, -C(=O)NHR⁶, -(CH₂)_pNHC(=O)R⁷, -O(CH₂)_qNR⁸R⁹, -OC₁₋₆alkylOH, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl or halogen;
- (b) oxazole;

R⁴ represents -C₆₋₁₀aryl;

R⁵ represents -H or -C₁₋₆alkyl;

R⁶ represents -H or -C₁₋₃alkyl or -C₁₋₃alkylOH;

R⁷ represents -H or -C₁₋₃alkyl;

R⁸ represents -H or -C₁₋₃alkyl;

R⁹ represents -H or -C₁₋₃alkyl;

m represents 1-3;

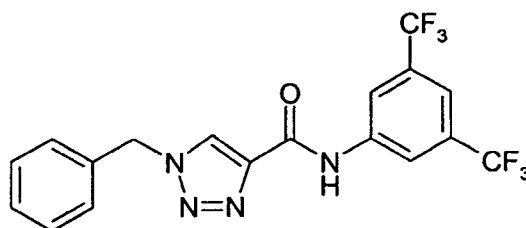
n represents 0-3;

p represents 0-3; and

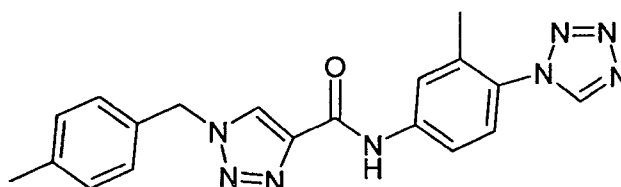
q represents 1-3;

or a pharmaceutically acceptable salt thereof;

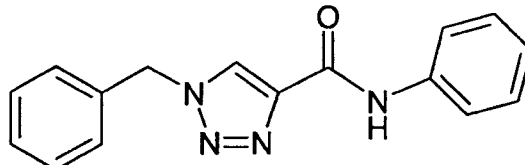
with the proviso that the compound of formula (I) is not
N-[3,5-bis(trifluoromethyl)phenyl]-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,



N-[2-(5-methyl-2-furanyl)phenyl]-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,



or, N-phenyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,



2. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1 wherein X represents -CONH- or -CH₂NH-.

3. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1 or claim 2 wherein R¹ represents phenyl optionally substituted by one, two or three groups independently selected from:

- (a) -C₁₋₆alkyl, -OCH₃, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, -C₃₋₆cycloalkyl, -OC₃₋₆cycloalkyl, or halogen;
- (b) phenyl optionally substituted by one, two or three groups independently selected from: halogen.

4. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 3 wherein R² represents -C₁₋₃alkyl.

5. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 wherein R^3 represents phenyl optionally substituted by one, two or three groups independently selected from:

- (a) $-C_{1-6}$ alkyl, $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkoxy, $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nCO_2R^5$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-6}$ alkylOH, $-C(=O)NHR^6$, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}$ alkylOH, $-C_{1-6}$ haloalkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-6}$ cycloalkyl, $-OC_{3-6}$ cycloalkyl or halogen;
- (b) oxazole.

6. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 wherein R^3 represents phenyl optionally substituted by:

- (i) one group independently selected from $-(CH_2)_nCO_2R^5$ or $-C(=O)NHR^6$ and/or,
- (ii) one, two or three groups independently selected from:
- (a) $-C_{1-6}$ alkyl, $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkoxy, $-O(CH_2)_mR^4$, $-(CH_2)_mOC(=O)R^4$, $-(CH_2)_nOC(=O)R^5$, $-C_{0-6}$ alkylOH, $-(CH_2)_pNHC(=O)R^7$, $-O(CH_2)_qNR^8R^9$, $-OC_{1-6}$ alkylOH, $-C_{1-6}$ haloalkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-6}$ cycloalkyl, $-OC_{3-6}$ cycloalkyl or halogen;
- (b) oxazole.

7. A compound of formula (I) according to claim 1 selected from:

N-[3,4-bis(methyloxy)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 N-[3,4-bis(methyloxy)phenyl]-1-[(4-bromophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 1-[(4-Fluorophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 1-[(4-Bromophenyl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 5-Methyl-1-(phenylmethyl)-N-{4-[(phenylmethyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
 1-[(2'-Chloro-4-biphenyl)yl)methyl]-5-methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1H-1,2,3-triazole-4-carboxamide,
 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
 5-Methyl-N-{4-[(3-methylbutyl)oxy]phenyl}-1-{4-(1-methylethyl)phenyl}methyl-1H-1,2,3-triazole-4-carboxamide,

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N-[3,4-Bis(methyloxy)phenyl]-5-methyl-1-[(4-methylphenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
1-(2-Biphenylmethyl)-N-[3,4-bis(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-Bis(methyloxy)phenyl]-1-[(4-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1,3-oxazol-2-yl)phenyl]-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-3-(methyloxy)benzoate,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[3-[(methylamino)carbonyl]phenyl]-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-[(methylamino)carbonyl]phenyl]-1H-1,2,3-triazole-4-carboxamide,
Ethyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]benzoate,
N-[3-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[4-(acetylamino)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-4-(methyloxy)benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-hydroxy-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Ethyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl]acetate,
Methyl 4-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-(methyloxy)benzoate,
Methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-hydroxybenzoate,
Methyl 3-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]phenyl]acetate,
1-[(3,4-Dichlorophenyl)methyl]-N-(3-hydroxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 5-[(1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)carbonyl]amino]-2-fluorobenzoate,

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N-[5-(Aminocarbonyl)-2-(methyloxy)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 4-chloro-3-[[1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]benzoate,
Methyl [3-[[1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]-4-(methyloxy)phenyl]acetate,
Methyl 3-[[1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]-4-fluorobenzoate,
N-[3-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[4-(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Methyl 3-[[1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]-4-(methyloxy)benzoate,
1-[(3,5-Dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-2-methylphenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3-[(Acetylamino)methyl]phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[4-chloro-3-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
Dimethyl 4-[[1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]-1,2-benzenedicarboxylate,
Methyl 5-[[1-[(3,5-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]-2-fluorobenzoate,
Ethyl 4-[[1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,5-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,

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1-[(3,4-Dichlorophenyl)methyl]-N-[5-(2-hydroxyethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[2-fluoro-5-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[2-chloro-5-(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,5-Dichlorophenyl)methyl]-N-[5-(hydroxymethyl)-2-(methyloxy)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-Bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,5-Dichlorophenyl)methyl]-N-[4-fluoro-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(2-hydroxyethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
3-[[[1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]benzoic acid,
3-[[[1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]-4-(methyloxy)benzoic acid,
5-[[[5-Methyl-1-(phenylmethyl)-1H-1,2,3-triazol-4-yl]carbonyl]amino]-1,3-benzenedicarboxylic acid,
4-[[[1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]benzoic acid,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-[(ethylamino)carbonyl]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-[(2-hydroxyethyl)amino]carbonyl]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[5-[(methylamino)carbonyl]-2-(methyloxy)phenyl]-1H-1,2,3-triazole-4-carboxamide,
3-[[[1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]phenyl}methyl acetate,
3-[[[1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]phenyl}methyl acetate,
3-[[[1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]phenyl}methyl benzoate,
3-[[[1-[(3,5-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl]carbonyl]amino]phenyl}methyl benzoate,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-[(2-hydroxyethyl)oxy]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,

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1-[(3,4-Dichlorophenyl)methyl]-5-methyl-N-[4-(1-methylethenyl)-2-(methoxy)phenyl]-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-(1-hydroxy-1-methylethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[4-{[2-(dimethylamino)ethyl]oxy}-3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-Dichlorophenyl)methyl]-N-[3-[(2-hydroxyethyl)oxy]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, and
{5-[(1-[(3,4-Dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl)methyl]amino}benzene-1,3-diyl}dimethanol,
or a pharmaceutically acceptable salt thereof.

8. A compound of formula (I) according to claim 1 selected from:
N-[3,4-bis(hydroxymethyl)phenyl]-5-methyl-1-(phenylmethyl)-1H-1,2,3-triazole-4-carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-chlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-bis(hydroxymethyl)phenyl]-1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
N-[3,4-bis(hydroxymethyl)phenyl]-1-[(3-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3-chlorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(4-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3-chlorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3-fluorophenyl)methyl]-N-[3-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide
1-[(4-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3-fluorophenyl)methyl]-N-[4-(hydroxymethyl)phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide,
1-[(3,4-dichlorophenyl)methyl]-N-[3-(hydroxymethyl)-5-[(methylamino)carbonyl]phenyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide, and
N-{1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}-4-(hydroxymethyl)benzamide
or a pharmaceutically acceptable salt thereof.

9. A compound of formula (I) according to claim 1 which is N-[3,5-bis(hydroxymethyl)phenyl]-1-[(3,4-dichlorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxamide or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 together with at least one pharmaceutical carrier and/or excipient.

11. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for use in therapy.

12. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for the manufacture of a medicament for treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

13. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 12 for the manufacture of a medicament for treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 12 for the manufacture of a medicament for treating and/or preventing acne, psoriasis, skin ageing, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 12 for the manufacture of a medicament for treating and/or preventing acne.

16. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for use in treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

17. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 16 for use in treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42.

18. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 16 for use in treating and/or preventing acne, psoriasis, skin ageing, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

19. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 16 for use in treating and/or preventing acne.

20. A method of treating and/or preventing a disease or a condition susceptible to amelioration by an SCD comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9.

21. A method of treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia,

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hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, skin ageing, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising A β 42 comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 20.

22. A method of treating and/or preventing acne, psoriasis, skin ageing, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH) comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 20.

23. A method of treating and/or preventing acne, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 20.

24. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 in combination with one or more active agent(s) selected from an inhibitor of cholesteryl ester transferase (CETP inhibitors), a HMG-CoA reductase inhibitor, a microsomal triglyceride transfer protein, a peroxisome proliferator-activated receptor activator (PPAR), a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an inhibitor of AcylCoA: cholesterol acyltransferase (ACAT inhibitor), a cannabinoid 1 antagonist and a bile acid sequestrant.

25. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 in combination with one or more active agent(s) selected from a corticosteroid, a vitamin D3 derivative, a retinoid, an immunomodulator, an anti androgen, a keratolytic agent, an anti-microbial, a platinum chemotherapeutic, an antimetabolite, hydroxyurea, a taxane, a mitotic

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disrupter, an anthracycline, dactinomycin, an alkylating agent and a cholinesterase inhibitor.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DCG/PB62693	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2008/065104	International filing date (day/month/year) 07/11/2008	(Earliest) Priority Date (day/month/year) 09/11/2007
Applicant SMITHKLINE BEECHAM CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the title,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

1,2,3-TRIAZOLE DERIVATIVES FOR USE AS STEAROYL-COA DESATURASE INHIBITORS

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D249/04 C07D413/12 A61K31/4192 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E (D5)	WO 2008/138917 A (NEUROSEARCH AS [DK]; NARDI ANTONIO [DK]; CHRISTENSEN JEPPE KEJSER [DK]) 20 November 2008 (2008-11-20) claims 1,11; examples 3,22	1-6, 10-14, 16-18, 20-22
P,X (D6)	WO 2008/073461 A (WYETH CORP [US]; GALULLO VINCENT [US]; ZELLE ROBERT [US]; MAZDIYASNI H) 19 June 2008 (2008-06-19) page 179, lines 16,17 -/-	1-6

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

5 February 2009

Date of mailing of the international search report

20/02/2009

Name and mailing address of the ISA/

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Authorized officer

Johnson, Claire

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X P, X (D1)	CALDERONE, V. ET AL.: "1,2,3-Triazol-carboxanilides and 1,2,3-triazol-(N-benzyl)-carboxamides as BK-potassium channel activators. XII" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 11, 7 March 2008 (2008-03-07), pages 2618-2626; XP002513784 7a-d; 8a-d; 12a,b,d; 13a,b,d; 14a,b,d; 15-19; <i>Relevant for FF claims only</i>	1-6, 10, 11
X X (D2)	----- DATABASE REGISTRY [Online] Chemical Abstracts Services, Columbus, Ohio, USA; 10 October 2007 (2007-10-10), XP002513785 Registry number 950075-10-2; 1H-1,2,3-Triazole-4-carboxamide, N-(2-methoxy-5-methylphenyl)-1-(phenylmeth yl)-; Supplier: Enamine	1-6
X X (D3)	----- DATABASE REGISTRY Chemical Abstracts Services, Columbus, Ohio, USA; 10 October 2007 (2007-10-10), XP002513786 Registry number 949879-07-6; 1H-1,2,3-Triazole-4-carboxamide, N-(4-bromo-2-methylphenyl)-1-(phenylmeth yl)-; Supplier: Enamine	1-6
X X (D4)	----- DATABASE REGISTRY Chemical Abstracts Services, Columbus, Ohio, USA; 23 April 2007 (2007-04-23), XP002513787 Registry number 931967-53-2; 1H-1,2,3-Triazole-4-carboxamide, N-[2-(5-methyl-2-furanyl)phenyl]-1-[(4-met hylphenyl)methyl]-; Supplier: Aurora Fine Chemicals	1-6
X A (D5)	----- WO 2005/011657 A (XENON PHARMACEUTICALS INC [CA]; SVIRIDOV SERGUEI [CA]; KODUMURU VISHNU) 10 February 2005 (2005-02-10) cited in the application claims 1,36 -----	1-18

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2008138917	A	20-11-2008	NONE	
WO 2008073461	A	19-06-2008	NONE	
WO 2005011657	A	10-02-2005	AU 2004261268 A1 BR PI0412348 A CA 2533901 A1 CN 1829698 A CN 1829701 A EC SP066311 A EP 1651620 A2 JP 2007500720 T KR 20060037409 A SG 145701 A1 US 2006252767 A1	10-02-2005 05-09-2006 10-02-2005 06-09-2006 06-09-2006 28-07-2006 03-05-2006 18-01-2007 03-05-2006 29-09-2008 09-11-2006

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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To:

GLAXOSMITHKLINE
Attn. Reed, Michael A.
Corporate Intellectual Property (CH925.1)
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

DCG

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

YR

23/2 (PCT Rule 44.1)

Date of mailing
(day/month/year)

20/02/2009 13 ✓

Applicant's or agent's file reference

DCG/PB62693

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP2008/065104

International filing date
(day/month/year)

07/11/2008

Applicant

SMITHKLINE BEECHAM CORPORATION

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



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

Authorized officer

Federico Bonomelli

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

9277

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2008/065104

International filing date (day/month/year)
07.11.2008

Priority date (day/month/year)
09.11.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D249/04 C07D413/12 A61K31/4192 A61P3/06

Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion 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 Rule 43bis.1(a)(i) 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

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

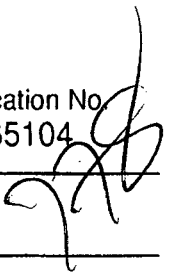
Johnson, Claire

Telephone No. +49 89 2399-5932



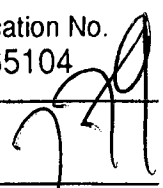
**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2008/065104



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:



Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>7-25</u>
	No: Claims	<u>1-6</u>
Inventive step (IS)	Yes: Claims	<u>7-25</u>
	No: Claims	<u>1-6</u>
Industrial applicability (IA)	Yes: Claims	<u>1-25</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

V. Reasoned statement

^{D2}
^{D3}
The compounds having the registry numbers 950075-10-2, 949879-07-6 and ^{D4} 931967-53-2, cited in the search report as "X", anticipate the subject matter of present claims 1-6. ✓

*Can amend
form!*

The technical problem underlying the present claims is the provision of inhibitors of stearyl-CoA desaturase (SCD). Document WO2005/011657 (hereafter known as D1) describes compounds with this activity. However, the compounds of D1 differ significantly from those of the present application, in particular lacking the present triazole ring attached to an aryl ring via a methylene group. No documents have been found which would have encouraged the skilled person starting from the compounds of D1, to perform the extensive modifications necessary to arrive at the present compounds, in the expectation that the qualitative activity would be maintained. Those of the present compounds which are novel may therefore be regarded as inventive.

*no amend
needed
Novel*

The present claims fulfil the requirements of industrial applicability. However, claims 20-23 relate to medical methods. The EPO does not recognise as patentable claims to the use of a compound in medical treatment, but allows claims to a product for use in a first or further medical treatment.

VI. Certain documents cited

^{D5}
✓ *Come
back
to* WO2008/138917 has an earlier priority date than the present priority date and was published after the present filing date. This document discloses compounds of a general formula (I) overlapping with the present general formula, as well as two specific compounds (3 and 22), for use in the treatment of conditions disclosed in present claim 21.

^{D6}
*amend
form* WO2008/073461 has an earlier priority date than the present priority date and was published between the present priority date and the present filing date. This document discloses a compound (p. 179, l. 16-17) falling within the scope of the present claims, used as an intermediate.

Should these documents enter the regional phase of examination, they would be

highly relevant for the regional phase of examination of the present document.

✓ Calderone et al., Eur. J. Med. Chem. 43 2008 2618-2626 discloses compounds 7a-d; 8a-d; 12a,b,d; 13a,b,d; 14a,b,d; 15-19; falling within the scope of present claims 1-6 and their use as biologically active molecules. Should the present claims not validly claim priority, this document would be highly relevant for the examination in the regional phase.

not relevant

Not relevant
→ claim 1 scope fully entitled to priority
→ and examples cited different to those examples recited @ FF (ex 89-93)

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/065104

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D249/04 C07D413/12 A61K31/4192 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2008/138917 A (NEUROSEARCH AS [DK]; NARDI ANTONIO [DK]; CHRISTENSEN JEPPE KEJSER [DK]) 20 November 2008. (2008-11-20) claims 1,11; examples 3,22 -----	1-6, 10-14, 16-18, 20-22
P,X	WO 2008/073461 A (WYETH CORP [US]; GALULLO VINCENT [US]; ZELLE ROBERT [US]; MAZDIYASNI H) 19 June 2008 (2008-06-19) page 179, lines 16,17 ----- -/--	1-6

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

5 February 2009

Date of mailing of the international search report

20/02/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Johnson, Claire

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/065104

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CALDERONE, V. ET AL.: "1,2,3-Triazol-carboxanilides and 1,2,3-triazol-(N-benzyl)-carboxamides as BK-potassium channel activators. XII" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 11, 7 March 2008 (2008-03-07), pages 2618-2626, XP002513784 7a-d; 8a-d; 12a,b,d; 13a,b,d; 14a,b,d; 15-19; -----	1-6, 10, 11
X	DATABASE REGISTRY [Online] Chemical Abstracts Services, Columbus, Ohio, USA; 10 October 2007 (2007-10-10), XP002513785 Registry number 950075-10-2; 1H-1,2,3-Triazole-4-carboxamide, N-(2-methoxy-5-methylphenyl)-1-(phenylmeth yl)-; Supplier: Enamine -----	1-6
X	DATABASE REGISTRY Chemical Abstracts Services, Columbus, Ohio, USA; 10 October 2007 (2007-10-10), XP002513786 Registry number 949879-07-6; 1H-1,2,3-Triazole-4-carboxamide, N-(4-bromo-2-methylphenyl)-1-(phenylmethyl)-; Supplier: Enamine -----	1-6
X	DATABASE REGISTRY Chemical Abstracts Services, Columbus, Ohio, USA; 23 April 2007 (2007-04-23), XP002513787 Registry number 931967-53-2; 1H-1,2,3-Triazole-4-carboxamide, N-[2-(5-methyl-2-furanyl)phenyl]-1-[(4-met hylphenyl)methyl]-; Supplier: Aurora Fine Chemicals -----	1-6
A	WO 2005/011657 A (XENON PHARMACEUTICALS INC [CA]; SVIRIDOV SERGUEI [CA]; KODUMURU VISHNU) 10 February 2005 (2005-02-10) cited in the application claims 1,36 -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/065104

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008138917 A	20-11-2008	NONE	
WO 2008073461 A	19-06-2008	NONE	
WO 2005011657 A	10-02-2005	AU 2004261268 A1 BR PI0412348 A CA 2533901 A1 CN 1829698 A CN 1829701 A EC SP066311 A EP 1651620 A2 JP 2007500720 T KR 20060037409 A SG 145701 A1 US 2006252767 A1	10-02-2005 05-09-2006 10-02-2005 06-09-2006 06-09-2006 28-07-2006 03-05-2006 18-01-2007 03-05-2006 29-09-2008 09-11-2006



No. 10-054279-00000-0000

Fecha: 2010-05-06 16:40:22
Tra. 11 PATENTEIYII
Act. 411 PRESENTACION

Dep. 2020 DIR.NUEVASCR
Eve: 378 FASENACIONALI
Folios: 289

PATENTE DE INVENCION ☐

MODELO D. ☐

Art 33 Decisión 486/00

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

PATENTE DE INVENCION PCT ☒

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

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

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
 - ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
 - ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
 - ☐ Comprobante de pago de las tasas establecidas
- Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
 - ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
 - ☐ Representación gráfica de un esquema de trazado
 - ☐ Comprobante de pago de las tasas establecidas
- Completa ☐ Incompleta ☐



Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
GLAXOSMITHKLINE LLC

REFERENCIA	Radicación No.	10 054279
	Solicitud internacional	PCT/EP2008/065104
	Fecha inicio fase nacional	09/06/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	Nº 08920

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 el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.
2. Debe aclarar el nombre del solicitante, por cuanto la publicación internacional difiere del petitorio presentado en fase nacional.
3. 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, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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.

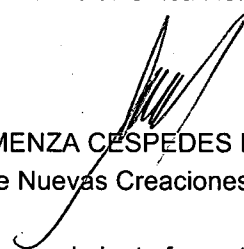
Continúa en la página siguiente...



Continuación radicado No: 10 054279



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 CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha
adpa11

16 JUL. 2010



Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
GLAXOSMITHKLINE LLC

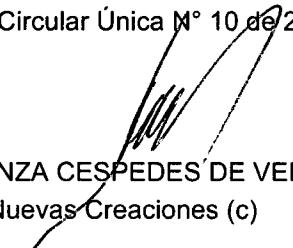
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	Solicitud internacional	PCT/EP2008/065104
	Fecha inicio fase nacional	09/06/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

08921

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única M° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 16 JUL. 2010
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