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INVENTARIO

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 07-81262

54. **TITULO** DERIVADOS NO ANILÍNICOS DE 1;1-DIÓXIDOS DE ISOTIAZOL-3(2H)
-ONA COMO MODULADORES DE RECEPTOR X HEPÁTICO

51. **CLASIFICACION INTERNACIONAL** A61K 31/425
A61K 31/5377
A61P 25/28
C07D 275/03

71. **SOLICITANTE** ASTRAZENECA AB

DOMICILIO SÖDERTÄLJE, SUECIA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.**

PETITORIO

AS: 104.416

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-081262- -00000-0000
Fecha: 2007-08-09 15:59:49 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 692

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

10/ago/2007

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: S-1-51 85 Södertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail	**IDENTIFICACIÓN** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: **JUAN PABLO CADENA SARMIENTO** Dirección: Cra. 7 No. 71-21 Torre B – Piso 4 Bogotá, Colombia Teléfono: 744-2200 Fax: 742-2200 E-mail:	**IDENTIFICACIÓN** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre**: Anders BROO, Patrik HOLM, Robert JUDKINS, Lanna LI, Eva-Lotte LINDSTEDT-ALSTERMARK, Pernilla SANDBERG, Marianne SWANSON, Lars WEIDOLF, Kay BRICKMANN. **Dirección:** AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; Skärgårdsvägen 984, FIN-21600 Pargas, FI; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca, R & D Molndal, SE-431 83 Molndal, SE (Respectivamente). **Nacionalidad o Domicilio**: Suecia (Respectivamente).	

5 PCT (86)

Solicitud Internacional No. PCT/SE2006/000029 Fecha 09-01-2006
Publicación Internacional No. WO 2006/073366 A1 Fecha 13-07-2006

6 Título (54): DERIVADOS NO ANILÍNICOS DE 1,1-DIÓXIDOS DE ISOTIAZOL-3(2H)-ONA COMO MODULADORES DE RECEPTOR X HEPÁTICO C07D 275/03

7 Clasificación Internacional (51): A61K 31/425 // 31/5377 // A61 P25/28

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	SE	10-01-2005	0500055-9

9 Comprobante de pago No. 07–50,862 **Fecha** 08-08-2007

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

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $482.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros Tarjeta de Propietarios
  Extracto para Publicacion y Tarjeta de Archivo Tematico
  Documentos PCT

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA: _____

C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

As 104.416

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-081262- -00000-0000

Fecha: 2007-08-09 15:59:49 Dep: 2020 NUECREACION
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 50,062
FECHA : JUNIO 25 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	59073666	25/06/2007	19,580,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Retiro folios 4 y 5 "Tarjetas"

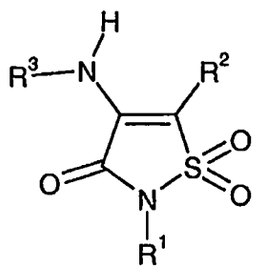
Industria y Comercio
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(1) N° de solicitud: (22) Fecha de solicitud: 30 Prioridad (31) No. Prioridad (32) Fecha (33) Pais 0500055-9 10-01-2005 SE	(51) Int Cl: (71) Solicitante (s): **ASTRAZENECA AB** (72) Inventor (es): Anders BROO, Patrik HOLM, Robert JUDKINS, Lanna LI, Eva-Lotte LINDSTEDT-ALSTERMARK, Pernilla SANDBERG, Marianne SWANSON, Lars WEIDOLF, Kay BRICKMANN. (74) Agente: JUAN PABLO CADENA SARMIENTO
(85) Fecha inicio fase nacional: 10-08-2007 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 09-01-2006 No. de solicitud: PCT/SE2006/000029	(87) Publicación internacional Fecha: 13-07-2006 N° publicación: WO 2006/073366 A1
(54) Titulo: DERIVADOS NO ANILÍNICOS DE 1,1-DIÓXIDOS DE ISOTIAZOL-3(2H)-ONA COMO MODULADORES DE RECEPTOR X HEPÁTICO	

Resumen:

La presente invención se refiere a ciertos compuestos novedosos de la fórmula (I)



Fórmula (I)

a procesos para preparar tales compuestos, a su utilidad en la modulación de receptores hormonales nucleares Receptor X Hepático (LXR)α (NR1H3) y/o β (NR1H2) y en tratar y/o prevenir enfermedades, incluidas enfermedades cardiovasculares tales como aterosclerosis; enfermedades inflamatorias, enfermedad de Alzheimer, trastornos lipídicos (dislipidemias) asociados o no con resistencia a la insulina, diabetes tipo 2 y otras manifestaciones del síndrome metabólico, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.

104-416 S

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

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(43) International Publication Date
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C07D 275/03 (2006.01)	*A61K 31/5377* (2006.01)
A61K 31/425 (2006.01)	*A61P 25/28* (2006.01)
A61K 31/427 (2006.01)	*A61P 3/06* (2006.01)
A61K 31/4427 (2006.01)	*A61P 3/10* (2006.01)
A61K 31/454 (2006.01)	*A61P 9/00* (2006.01)
A61K 31/4545 (2006.01)	*A61P 9/10* (2006.01)
A61K 31/506 (2006.01)	*C07D 417/12* (2006.01)

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0500055-9 10 January 2005 (10.01.2005) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BROO, Anders** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **HOLM, Patrik** [FI/FI]; Skärgårdsvägen 984, FIN-21600 Pargas (FI). **JUDKINS, Robert** [GB/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **LI, Lanna** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **LINDSTEDT-ALSTERMARK, Eva-Lotte** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **SANDBERG, Pernilla** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **SWANSON, Marianne** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **WEIDOLF, Lars** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **MRICKMANN, Kay** [DE/SE]; AstraZeneca, R & D Molndal, SE-431 83 Molndal (SE).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).

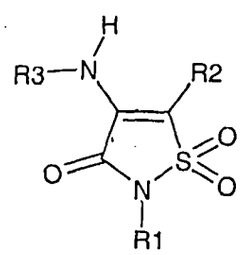
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, 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, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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

(54) Title: NON-ANILINIC DERIVATIVES OF ISOTHIAZOL-3(2H)-ONE 1,1-DIOXIDES AS LIVER X RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention relates to certain novel compounds of the formula (I) to processes for preparing such compounds, to their the utility in modulation of nuclear hormone receptors Liver X Receptor (LXR) α (NR1H3) and/or β (NR1H2) and in treating and/or preventing clinical conditions including cardiovascular diseases such as atherosclerosis; inflammatory diseases, Alzheimer's disease, lipid disorders (dyslipidemias) whether or not associated with insulin resistance, type 2 diabetes and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

WO 2006/073366 A1

AS: 104416
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AstraZeneca

WIPO - World Intellectual Property Organization
34, Chemin des Colombettes
CH-1211 GENEVE 20
Switzerland

4 June 2007

Our Ref
101613-1P WO

BY FAX - ORIGINAL BY MAIL

Re: Change of name of the inventor Kay BRICKMANN in International PCT Application PCT/SE2006/000029

Dear Sirs,

Please change the name of the inventor Kay MRICKMANN in the International PCT application PCT/SE2006/000029

into:

Kay BRICKMANN

We look forward to receiving the Form PCT/IB/306 as soon as possible.

Yours faithfully,

AstraZeneca AB
Global Intellectual Property

Sonya Celebioglu
IP Services Team Leader, Formalities

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NON-ANILINIC DERIVATIVES OF ISOTHIAZOL-3(2H)-ONE 1, 1-DIOXIDES AS LIVER X RECEPTOR MODULATORS

Field of the invention

The present invention relates to certain novel 4-(amino)isothiazol-3(2*H*)-one 1,1-dioxides, to processes for preparing such compounds, to their the utility in modulation of nuclear hormone receptors Liver X Receptor (LXR) α (NR1H3) and/or β (NR1H2) and in treating and/or preventing clinical conditions including cardiovascular diseases such as atherosclerosis; inflammatory diseases, Alzheimer's disease, lipid disorders (dyslipidemias) whether or not associated with insulin resistance, type 2 diabetes and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

Background of the invention

Abnormalities of cholesterol and fatty acid homeostasis, that are reflected as diverse dyslipidemias, are causal of atherosclerosis and consequently cardiovascular disease (CVD). This disease is one of the major health problems in industrialized countries and is reaching the same prevalence in adults in developing nations. Most studies show that statins reduce low density lipoproteins (LDL) cholesterol by 25-30% and the relative risk of coronary events by approximately 30%. While this beneficial effect is significant, effectively 70% of the treated cohort remains with unchanged risk. This has prompted intense research in order to identify other common abnormalities of lipid metabolism that if efficiently treated could improve the results of current CVD therapy.

The nuclear hormone receptors LXR α and β use oxysterols as natural ligands. They appear to act as cholesterol sensors with target genes that are required for cholesterol efflux from macrophages, like ATP binding cassette transporter A1 (ABCA1) and apoE, as well as gene products, like cholesterol ester transferase protein (CETP) and phospholipid transport protein (PLTP), that are required for the function of high density lipoprotein (HDL) in the reverse cholesterol transport. In the liver, LXR ligands seem to stimulate the hepatobiliary secretion of cholesterol, a pathway controlled by the ABCG5 and ABCG8. The same cholesterol transporters appear to reduce cholesterol absorption in enterocytes, therefore influencing total

body cholesterol balance. These effects of LXR stimulation could help to explain its remarkable anti-atherosclerotic properties observed in animal models.

Recently the synthetic LXR ligands GW3965 (Glaxo) and T-0901317 (Tularik) were reported to increase glucose tolerance in fat fed obese mouse, which was interpreted to result from reduced hepatic gluconeogenesis and increased glucose uptake in adipocytes Lafitte BA et al. (Proc Natl Acad Sci U S A. 2003 Apr 29;100(9):5419-24). Activation of LXR's improves glucose tolerance through coordinated regulation of glucose metabolism in liver and adipose tissue.

JP2001163786A discloses the synthesis of certain novel 2-(substituted alkyl)-4-(substituent)-5-(substituent)isothiazol-3(2*H*)-one 1,1-dioxides wherein the 4- or 5-positions are substituted by e.g. H, lower alkyl or carboxyl. These compounds are reported to have matrixmetalloproteinase (MMP) inhibitory activity (especially matrixmetalloproteinase-13 (MMP-13) inhibitory activity) and aggrecanase inhibitory activity, and are useful in the prevention or treatment of arthritis (especially osteoarthritis) and for inhibiting metastasis, infiltration or proliferation of cancer (especially breast cancer).

EP1069110A1 discloses the synthesis of certain novel 2-(substituted alkyl)-4-(substituent)-5-(substituent)isothiazol-3(2*H*)-one 1,1-dioxides wherein the 4- or 5-positions are substituted by e.g. H, lower alkyl or carboxyl. These compounds are reported to have matrixmetalloproteinase-13 (MMP-13) inhibitory activity and aglycanase inhibitory activity, and are useful for treating arthritic disorders such as reumatoid arthritis.

WO9708143A1 discloses the synthesis of 2-(substituted alkyl)-4-(substituent)-5-(substituent)isothiazol-3(2*H*)-one 1,1-dioxides wherein the substituents in 4- or 5-positions are selectioned from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, carbamoyl substituted with an alkyl of 1 to 3 carbon atoms, acetoxy, carboxy, hydroxy, amino, amino substituted with an alkyl of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halo, or the 4 and/or 5 positions are unsubstituted, and their use for reducing levels of Tumor Necrosis Factor (TNF) in mammals.

In the application WO05/005417 it is disclosed that certain novel 1-(substituted alkyl)-3 amino-4 phenyl-1*H*-pyrrole-2,5-dione derivatives have utility in the modulation of nuclear hormone receptors Liver X Receptor (LXR) α (NR1H3) and/or β (NR1H2) and in treating and/or preventing clinical conditions including cardiovascular diseases.

In the application WO05/005416 it is disclosed that certain novel 5-thioxo-1,5-dihydro-2*H*-pyrrol-2-one and 1*H*-pyrrole-2,5-dithione derivatives have utility in the modulation of nuclear hormone receptors Liver X Receptor (LXR) α (NR1H3) and/or β (NR1H2) and in treating and/or preventing clinical conditions including cardiovascular diseases.

WO05/035551 discloses certain novel 2-(substituent)-4-(substituent)-5-(substituent)isothiazol-3(2*H*)-one 1,1-dioxides. These compounds are reported to modulate the activity of a target protein such as a phosphatase.

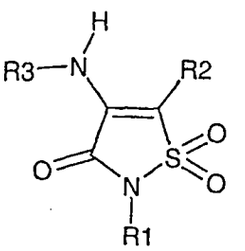
The term "LXR modulator" as used herein more specifically means a compound with the ability to modulate the biological activity of LXRα and/or LXRβ via increase or decrease of the function and/or expression of LXRα and/or LXRβ, where LXRα and/or LXRβ function may include transcription regulatory activity and/or protein-binding. Modulation may occur *in vitro* or *in vivo*. Modulation, as described herein, includes antagonism, agonism, partial antagonism and/or partial agonism of a function or characteristic associated with LXRα and/or LXRβ, either directly or indirectly, and/or the upregulation or downregulation of LXRα and/or LXRβ expression, either directly or indirectly. More specifically, such an LXR modulator either enhances or inhibits the biological activities of LXR via the function and/or expression of LXR. If such a modulator partially or completely enhances the biological activities of LXR via the function and/or expression of LXR, it is a partial or full LXR agonist, respectively. It is the object of the present invention to provide LXR modulators. Another object of this invention is to provide LXR modulator compounds being LXR agonists.

It should be noted that to show activity in the specific Test Methods described herein, the LXR modulator compound must bind to the ligand binding domain of the LXR and recruit either the specific peptide derived from the co-activator protein, SRC1, to the modulator compound-bound LXR complex in the described Co-activator recruitment assay, or one or more of the nuclear hormone receptor co-factors present in for example the U2OS cell-based

method described herein. The compounds of this invention that form an LXR-modulator compound-complex may recruit at least one or more of the other >80 known different nuclear hormone receptor cofactors in any other cell-based method prepared and assayed according to known procedures. Compounds according to formula (I), that do not recruit the SRC1-derived peptide or any of the co-factors present in the in cell-based method described herein, is however anticipated to bind to LXR and the LXR-modulator compound-complex so formed will recruit at least one or more of the other >80 known different nuclear receptor cofactors present in other cellular system. The LXR modulator compound-complex may also displace co-repressors, such as NcOR, with simultaneous recruitment of a co-activator or may only displace a co-repressor without co-activator recruitment, leading to partial activation of certain LXR regulated genes. Recruiter peptides derived from any of these other nuclear hormone receptor cofactors may be similarly prepared and assayed according to known procedures.

Description of the invention

According to a first aspect of the invention there is provided a compound of formula I:



formula I

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

cycloalkyl or heterocyclyl each optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a,

OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

phenyl or heteroaryl each optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

R^2 represents

phenyl which is optionally substituted byone or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$,

$NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the folowing: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

The following definitions shall apply throughout the specification and the appended claims unless specifically stated otherwise:

The term "X" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein said alkyl group may optionally be interrupted by O, S, SiR^bR^b, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2. It shall be understood that when X is present more than once in the same compound then the value may be the same or different. Examples of said "X" include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl, vinyl, isopropenyl, allyl, but-2-enyl, ethynyl, 2-propynyl, 2-methoxyethyl, 3-methylpropyl, methylthiomethyl, 3-hydroxypropyl, 2-(2-methoxyethoxy)ethyl, 3-(2-methoxyethoxy)propyl, 2,2-dimethylpropyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, 2,3-dihydroxypropyl, 2-cyanoethyl and methyl ethanoylglycinate.

The term "Y" denotes a straight or branched, saturated or unsaturated alkylene group having 1 to 3 carbon atoms wherein said alkylene group binds to nitrogen in 2-position in the isothiazol-3(2*H*)-one 1,1-dioxide and may optionally be interrupted or ended by one of the following: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c and/or Y is optionally substituted by one or more of the following independently selected from: OH, F, CN, NR^aR^a, C_1-C_4alkyl, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$ or SO_2R^b. In the definition of "Y" the term "ended by O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c" means that the alkylene group has as the last position O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$ or NR^c before it binds further to phenyl, heteroaryl, cycloalkyl or heterocyclyl. Examples of said "Y" include, but are not limited to, methylene, ethylene, propylene, 2-methylethylene, and 1-methylethylene.

The term "Z" denotes a straight or branched, saturated or unsaturated alkylene group having 1 to 6 carbon atoms wherein said alkylene group binds to E or Het^4 and one of the following: Q, Het^1, R or Het^2, and may optionally be interrupted or ended by one of the following: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $C(O)CR^a$, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, or is one of the following: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a , SO_2NR^a, NR^aSO_2 and/or Z is optionally substituted by one or more of the following independently selected from: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $SiR^bR^bR^b$, $S(O)R^c$, SO_2R^c, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, OR^b. In the definition of "Z" the term "ended by O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2" means that the alkylene group has as the last position O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a or NR^aSO_2 before it binds further to E, Het^4, Q, Het^1, R or Het^2. Examples of said "Z" include, but are not limited to, methylene, ethylene, propylene, butylene, pentylene, hexylene, O, S, S(O), SO_2, C(O), OC(O), C(O)O, $C(O)CH_2$, $CH_2C(O)$, $C(O)(C_1$-C_4alkyl), NHC(O), C(O)NH, NH, SO_2NH, $NHSO_2$, $N(C_1$-C_4alkyl)C(O), $C(O)N(C_1$-C_4alkyl), $N(C_1$-C_4alkyl) , $SO_2N(C_1$-C_4alkyl), $N(C_1$-C_4alkyl)SO_2, 1-methylpropylene, 2-methylpropylene and 3-methylpropylene. In the definition of Z it is to be understood that specific values bind in the order written, i.e. from left to right. For example, when Z is $C(O)CH_2$ then C(O) in said $C(O)CH_2$ binds to E or Het^4 and CH_2 in said $C(O)CH_2$ binds to Q, Het^1, R or Het^2.

The term "M" denotes a saturated or unsaturated non-aromatic monocarbocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring system composed of 8, 9 or 10 carbon atoms. Examples of said "M" include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl, cyclooctadienyl, decaline, hydrindane, indane, indene, and bicyclo[4.2.0]octa-1,3,5-triene.

The term "E" denotes a saturated or unsaturated non-aromatic monocarbocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring system composed of 8, 9 or 10 carbon atoms. The ring binds,

unless otherwise specified, through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide. Examples of said "E" include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl, cyclooctadienyl, decaline, hydrindane, indane, indene and bicyclo[4.2.0]octa-1,3,5-triene.

The term "A" denotes an aromatic monocyclic ring composed of 6 carbon atoms or an aromatic bicyclic ring system composed of 10 carbon atoms. Examples of said "A" include, but are not limited to, phenyl, naphtalene and azulene.

The term "P" denotes a straight or branched, saturated or unsaturated alkylene group having 1 to 6 carbon atoms wherein the alkylene group binds to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide and is optionally interrupted or ended by one of the following: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 and/or P is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or OR^b. In the definition of "P" the term "ended by O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2" means that the alkylene group has as the last position O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2" before it binds further to M, Het^3, A or Het^5. Examples of said "P" include, but are not limited to, methylene, ethylene, propylene, butylene, ethyleneoxy, propyleneoxy, butyleneoxy, ethyleneamino, ethylenethio, propylenethio, $CH_2C(O)NHCH_2$, $CH_2C(O)O$, $CH_2CH_2C(O)O.CH_2CH_2CH_2C(O)O$, $CH_2C(O)OCH_2$, $CH_2C(O)OCH_2CH_2$, $CH_2CH_2OCOCH_2$, $CH_2C(O)OCH(CH_3)CH_2$, 1-methylpropylene, 2-methylpropylene and 3-methylpropylene. In the definition of P it is to be understood that the specific values bind in the order written, i.e. from left to right. For example, when P is ethyleneoxy then it is the oxygen that binds to M, Het^3, A or Het^5.

The term "Q" denotes a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms, which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b,

$C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$. Examples of said "Q" include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl and cyclooctadienyl.

The term "R" denotes a phenyl group which is optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

The term "T" denotes methylene or is one of the following: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2. T binds to M, Het^3, A or Het^5 and one of the following: Q, Het^1, R or Het^2. Examples of said "T" include, but are not limited to, methylene, O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a and NR^aSO_2.

The term "C_1alkyl" denotes an alkyl group having 1 carbon atom. An example of said alkyl includes, but is not limited to, methyl.

The term "C_1-C_3alkyl" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 3 carbon atoms. Examples of said alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, vinyl, isopropenyl, allyl, ethynyl, and 2-propynyl.

The term "C_1-C_4alkyl" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 4 carbon atoms. Examples of said alkyl include, but are not limited to, methyl,

ethyl, propyl, isopropyl, tert-butyl, vinyl, isopropenyl, allyl, but-2-enyl, ethynyl, 2-propynyl, and but-2-ynyl.

The term "halogen" denotes fluoro, chloro, bromo and iodo groups.

The term "cycloalkyl" denotes a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms. For example, C_3-C_6cycloalkyl denotes a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5 or 6 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Further examples of said "cycloalkyl" include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl and cyclooctadienyl.

The term "heterocyclyl" denotes a saturated or unsaturated non-aromatic 3, 4, 5, 6, 7 or 8 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). Examples of said "heterocyclyl" include, but are not limited to, aziridine, azetidine, 2- pyrroline, 3-pyrroline, pyrrolidine, imidazoline, piperidine, piperazine, 2-pyrazoline, oxirane, oxetane, tetrahydrofuran, tetrahydropyran, 1,4-dioxane, 1,3-dioxolane, 1,2-oxathiolane, morpholine, 3-pyrazoline, pyrazolidine, 2H-pyrane, 4H-pyrane, 1,4-dithiane, 1,4-oxathiane and thiomorpholine.

The term "heteroaryl" denotes an aromatic 5 or 6 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon independently selected from one or more of for example nitrogen, oxygen and sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). Examples of said "heteroaryl" include, but are not limited to, furan, pyrrole, pyrazine, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, pyridine-1-oxide, isoxazole, oxazole, isothiazole, thiazole, thiophene, 1,2,4-triazole, furazane, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole and 1,2,3-thiadiazole.

The term "Het^1" denotes a saturated or unsaturated non-aromatic 3, 4, 5, 6, 7, 8, 9, or 10 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur, and wherein the ring optionally is substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). Examples of said "Het^1" include, but are not limited to aziridine, azetidine, 2- pyrroline, 3-pyrroline, pyrrolidine, imidazoline, piperidine, piperazine, 2-pyrazoline, oxirane, oxetane, tetrahydrofuran, tetrahydropyran, 1,4-dioxane, 1,3-dioxolane, 1,2-oxathiolane, morpholine, 3-pyrazoline, pyrazolidine, 2H-pyrane, 4H-pyrane, 1,4-dithiane, 1,4-oxathiane and thiomorpholine.

The term "Het^2" denotes an aromatic 5 or 6 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon independently selected from one or more of for example nitrogen, oxygen and sulfur, and which is substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). Examples of said "Het^2" include, but are not limited to, furan, pyrrole, pyrazine, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, pyridine-1-oxide, isoxazole, oxazole, isothiazole, thiazole, thiophene, 1,2,4-triazole, furazane, 1,2,3-oxadiazole, 1,2,4-

oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole and 1,2,3-thiadiazole.

The term "Het^3" denotes a saturated or unsaturated non-aromatic 3, 4, 5, 6, 7, 8, 9 or 10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 9 or 10 membered bicyclic ring system in which one or more of the atoms in the monocyclic ring or bicyclic ring system is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). Examples of said "Het^3" include, but are not limited to aziridine, azetidine, 2- pyrroline, 3-pyrroline, pyrrolidine, imidazoline, piperidine, piperazine, 2-pyrazoline, oxirane, oxetane, tetrahydrofuran, tetrahydropyran, 1,4-dioxane, 1,3-dioxolane, 1,2-oxathiolane, morpholine, 3-pyrazoline, pyrazolidine, 2H-pyrane, 4H-pyrane, 1,4-dithiane, 1,4-oxathiane, thiomorpholine, indoline, 1,3-dihydro-2-benzofuran, 2,3-dihydro-1-benzofuran, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, chroman and isochroman.

The term "Het^4" denotes a saturated or unsaturated non-aromatic 3, 4, 5, 6, 7, 8, 9 or 10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 9 or 10 membered bicyclic ring system in which one or more of the atoms in the monocyclic ring or bicyclic ring system is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). The ring binds, unless otherwise specified, through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide. Examples of said "Het^4" include, but are not limited to, aziridine, azetidine, 2- pyrroline, 3-pyrroline, pyrrolidine, imidazoline, piperidine, piperazine, 2-pyrazoline, oxirane, oxetane, tetrahydrofuran, furan, tetrahydropyran, 1,4-dioxane 1,3-dioxolane, 1,2-oxathiolane, morpholine, 3-pyrazoline, pyrazolidine, isoxazole, 2H-pyrane, 4H-pyrane, 1,4-dithiane, 1,4-oxathiane, thiomorpholine, indoline, 1,3-dihydro-2-benzofuran, 2,3-dihydro-1-benzofuran, 1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxine, chroman and isochroman.

The term "Het^5" denotes an aromatic 5 or 6 membered monocyclic ring or an aromatic 9 or 10 membered bicyclic ring in which one or more of the atoms in the monocyclic ring or bicyclic

ring system is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). Examples of said "Het^5" include, but are not limited to, furan, pyrrole, pyrazine, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, pyridine-1-oxide, isoxazole, oxazole, isothiazole, thiazole, thiophene, 1,2,4-triazole, furazane, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole 1,2,3-thiadiazole, benzofuran, isobenzofuran, indole, isoindole, benzothiophene, benzo[c]thiophene, benzimidazole, purine, indazole, benzoxazole, benzisoxazole, bnezthiazole, quinoline, quinoxaline, quinazoline, cinnoline and isoquionoline.

R^a independently represents H or a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F.

R^b independently represents a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F.

R^c independently represents H or a straight or branched, saturated or unsaturated C_1-C_3alkyl chain optionally substituted by one or more F.

It shall be understood that when a substitutent bears more than one of R^a, R^b or R^c then each of these may be the same or different. For example, NR^aR^a includes amino, alkylamino and dialkylamino. Furthermore, it shall be understood that when different substituents in the same compound bear more than one of R^a, R^b or R^c then each of these may be the same or different.

Further values of R^1, R^2 and R^3 in compounds of formula I now will follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In a first group of compounds of formula I

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally

substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

cycloalkyl or heterocyclyl each optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

phenyl or heteroaryl each optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

R^2 represents

phenyl which is optionally substituted byone or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more

of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$,

Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the folowing: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a second group of compounds of formula I

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

cycloalkyl or heterocyclyl each optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

phenyl or heteroaryl each optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 represents

phenyl which is optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

R^3 is the same as in the first group of compounds of formula I.

In a third group of compounds of formula I

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$,

R^2 is the same as in the second group of compounds of formula I,

R^3 is the same as in the first group of compounds of formula I.

In a fourth group of compounds of formula I

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b or $C(O)R^b$,

R^2 is the same as in the second group of compounds of formula I,

R^3 is the same as in the first group of compounds of formula I.

In a fifth group of compounds of formula I

R^1 is the same as in the first group of compounds of formula I,

R^2 is the same as in the first group of compounds of formula I, and

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a sixth group of compounds of formula I

R^1 is the same as in the first group of compounds of formula I,

R^2 is the same as in the first group of compounds of formula I, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen(F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a seventh group of compounds of formula I

R^1 is the same as in the first group of compounds of formula I,

R^2 is the same as in the first group of compounds of formula I, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$,

$OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In an 8th group of compounds of formula I

R^1 is the same as in the second group of compounds of formula I,

R^2 is the same as in the second group of compounds of formula I, and

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a 9th group of compounds of formula I

R^1 is the same as in the second group of compounds of formula I,

R^2 is the same as in the second group of compounds of formula I, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b,

$S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a 10th group of compounds of formula I

R^1 is the same as in the second group of compounds of formula I,

R^2 is the same as in the second group of compounds of formula I, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH,

CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

In an 11th group of compounds of formula I

R^1 is the same as in the third group of compounds of formula I,

R^2 is the same as in the third group of compounds of formula I, and

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a 12th group of compounds of formula I

R^1 is the same as in the third group of compounds of formula I,

R^2 is the same as in the third group of compounds of formula I, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a 13th group of compounds of formula I

R^1 is the same as in the third group of compounds of formula I,

R^2 is the same as in the third group of compounds of formula I, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

In a 14th group of compounds of formula I

R^1 is the same as in the fourth group of compounds of formula I,

R^2 is the same as in the fourth group of compounds of formula I, and

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally

substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a 15th group of compounds of formula I

R^1 is the same as in the fourth group of compounds of formula I,

R^2 is the same as in the fourth group of compounds of formula I, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a 16th group of compounds of formula I

R^1 is the same as in the fourth group of compounds of formula I,

R^2 is the same as in the fourth group of compounds of formula I, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

The compounds of formula I have activity as medicaments. In particular the compounds of formula (I) are LXR agonists.

In another aspect of the invention, there is provided a compound according to formula (V) in which R^1 is selected from ethyl, isopropyl, n-butyl, *tert*butyl, cyclopentyl, hexyl, benzyl, 2-methoxyethyl, pyridin-2ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, tetrahydrofuran-2-ylmethyl or 2-(3-fluorophenyl)ethyl; and
R^2 is phenyl.

In another aspect of the invention, there is provided a compound according to formula (VI) in which R^1 is selected from ethyl, isopropyl, n-butyl, *tert*butyl, cyclopentyl, hexyl, benzyl, 2-methoxyethyl, pyridin-2ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, tetrahydrofuran-2-ylmethyl or 2-(3-fluorophenyl)ethyl,
R^2 is phenyl and L is a leaving group such as for instance Cl, Br, I, methanesulfonate (MsO) or trifluoromethanesulfonate (OTf).

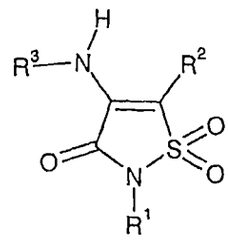
In one aspect of the invention there is provided a compound of formula (I) in which R^1 is selected from ethyl, isopropyl, n-butyl, *tert*butyl, cyclopentyl, hexyl, benzyl, 2-methoxyethyl, pyridin-2ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, tetrahydrofuran-2-ylmethyl or 2-(3-fluorophenyl)ethyl;

R^2 is phenyl; and

R^3 is selected from butyl, hexyl, benzyl, 3-[3-(hydroxymethyl)phenoxy]propyl, 4-phenylbutyl, 3-(2-methoxyphenoxy)propyl, 3-[4-(hydroxymethyl)phenoxy]propyl, 3-(2-fluorophenoxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(pyridin-3-yloxy)propyl, 3-(pyridin-4-yloxy)propyl, 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 3-(phenylthio)propyl, 3-phenoxypropyl, 3-(3-chlorophenoxy)propyl, 3-(3-fluorophenoxy)propyl, 3-(4-fluorophenoxy)propyl, 1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl, *cis*-4-hydroxycyclohexyl, 4-phenoxybutyl, 3-[(1-oxidopyridin-3-yl)oxy]propyl, 3-(4-methoxyphenoxy)propyl, 4,4-difluorocyclohexyl, 2-phenoxyethyl, 2-phenylethyl, 4-(difluoromethoxy)benzyl, *trans*-4-hydroxycyclohexyl, 3-hydroxypropyl, 2,3-dihydro-1,4-benzodioxin-2-ylmethyl, 4-hydroxycyclohexyl, 3-(4-chlorophenoxy)propyl, 1,3-benzodioxol-5-ylmethyl, 2,3-dihydro-1*H*-inden-2-yl, 2-(morpholin-4-yl)ethyl, 3-(4-isopropylphenoxy)propyl, 3-[benzyl(butyl)amino]propyl, 3-(3,5-dipropoxyphenoxy)propyl, 2,2-diphenylethyl, 2-(1*H*-imidazol-4-yl)ethyl
4-morpholin-4-ylbenzyl, 3-(2-methoxyethoxy)propyl, 3-morpholin-4-ylpropyl, 2-methoxyethyl, tetrahydro-2*H*-pyran-4-yl, 4-hydroxycyclohexyl, 4-methoxybenzyl, 3-(3-hydroxyphenoxy)propyl, 3-(3-acetamidophenoxy)propyl, 3-(4- *N,N*-dimethylaminocarbonylmethylphenoxy)propyl, 3-(3-carboxymethylphenoxy)propyl, 3-(3-methoxycarbonylmethylphenoxy)propyl, 3-(3-methoxycarbonylphenoxy)propyl, 3-(4-carboxymethylphenoxy)propyl, 3-(4-methoxycarbonylmethylphenoxy)propyl, 3-(3-acetylaminophenoxy)propyl, 3-(4-hydroxyphenylcarboxy)propyl, 3-(4-carboxyphenoxy)propyl or 1-(2-nitriloethyl)piperidin-4-yl.

Further embodiments of the invention

According to another embodiment of the invention there is provided a compound of general formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof,

wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

or R^1 is cycloalkyl or heterocyclyl each optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is phenyl or heteroaryl each optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

R^2 represents

phenyl which is optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$,$S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

or R^3 is MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$ $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b,

SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$,$S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further values of R^1, R^2 and R^3 will now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In a first embodiment of the invention there is provided a class of compounds of formula I wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$,

$NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

or R^1 is cycloalkyl or heterocyclyl each optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is phenyl or heteroaryl each optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following independently selected from:

halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

R^2 represents

phenyl which is optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$,$S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

or R^3 is

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$,

SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$ $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH,

CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$,$S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a second embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

or R^1 is cycloalkyl or heterocyclyl each optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

or R^1 is phenyl or heteroaryl each optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

or R^1 is cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

or R^1 is phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 represents

phenyl which is optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

R^3 is the same as for the first embodiment.

In a third embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$,

R^2 is the same as for the second embodiment , and

R^3 is the same as for the first embodiment.

In a fourth embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more

of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or $C(O)R^b$,

R^2 is the same as for the second embodiment, and

R^3 is the same as for the first embodiment.

In a fifth embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same for the first embodiment,

R^2 is the same as for the first embodiment, and

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a sixth embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the first embodiment,

R^2 is the same as for the first embodiment, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a seventh embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the first embodiment,

R^2 is the same as for the first embodiment, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b,

$C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the folowing independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In an 8th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the second embodiment,

R^2 is the same as for the second embodiment, and

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a 9th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the second embodiment,

R^2 is the same as for the second embodiment, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F,

OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a 10th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the second embodiment,

R^2 is the same as for the second embodiment, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In an 11th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the third embodiment,

R^2 is the same as for the third embodiment, and

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a 12th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the third embodiment,

R^2 is the same as for the third embodiment, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$,

$C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a 13th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the third embodiment,

R^2 is the same as for the third embodiment, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a 14th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the fourth embodiment,

R^2 is the same as for the fourth embodiment, and

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

In a 15th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the fourth embodiment,

R^2 is the same as for the fourth embodiment, and

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In a 16th embodiment of the invention there is provided a class of compounds of formula (I) wherein

R^1 is the same as for the fourth embodiment,

R^2 is the same as for the fourth embodiment, and

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$,

$C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

The compounds of formula (I) have activity as medicaments. In particular, the compounds of formula (I) are LXR agonists.

Specific compounds of the invention are one or more of the following:

2-*tert*-butyl-4-({3-[3-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(2-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({3-[4-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N-(3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide

2-*tert*-butyl-4-{[3-(2-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-(4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)-N,N-dimethylacetamide

2-*tert*-butyl-4-{[3-(2-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

(3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-3-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

methyl (3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-4-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-cyclopentyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[3-(phenylthio)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(3-phenoxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl 3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoate

2-benzyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

(4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

2-*tert*-butyl-4-{[3-(3-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl (4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

2-*tert*-butyl-4-{[3-(4-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-({1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

N-(3-{3-[(2-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide

3-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-hydroxybenzoate

4-(benzylamino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-[2-(3-fluorophenyl)ethyl]-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

4-[(cis-4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(4-phenoxybutyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({3-[(1-oxidopyridin-3-yl)oxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-cyclopentyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(4-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(4,4-difluorocyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(tetrahydrofuran-2-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-(hexylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-{[4-(difluoromethoxy)benzyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(trans-4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(3-hydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-3-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-hydroxycyclohexyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

3-{4-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}propanenitrile

2-*tert*-butyl-4-{[3-(4-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-4-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-(2,3-dihydro-1H-inden-2-ylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(2-morpholin-4-ylethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(4-isopropylphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({3-[benzyl(butyl)amino]propyl}amino)-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3,5-dipropoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,2-diphenylethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-ethyl-4-{[2-(1H-imidazol-4-yl)ethyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-morpholin-4-ylbenzyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-{[3-(2-methoxyethoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(3-morpholin-4-ylpropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(2-methoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-(2-methoxyethyl)-5-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide

4-(hexylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(4-hydroxycyclohexyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-methoxybenzyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-2-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-hydroxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzenesulfonamide

2-*tert*-butyl-4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

tert-butyl 3-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}azetidine-1-carboxylate

2-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

4-({4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}methyl)benzonitrile

2-*tert*-butyl-4-(isopropylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

tert-butyl 3-({2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}thio)pyrrolidine-1-carboxylate

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-2-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({1-[2-(trifluoromethyl)benzoyl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(5-methylpyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(6-chloropyridazin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

tert-butyl 4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidine-1-carboxylate

methyl 2-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}benzoate

methyl 3-({4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}methyl)benzoate

2-*tert*-butyl-4-{[1-(6-methoxypyridazin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

2-*tert*-butyl-4-{[1-(6-chloropyridin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(1-benzylpiperidin-4-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzenesulfonamide

4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

2-*tert*-butyl-4-(ethylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({1-[(5-methylisoxazol-3-yl)methyl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N^2-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-N^1-[3-(difluoromethoxy)benzyl]glycinamide

4-[(1-benzoylpiperidin-4-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[1-(phenylacetyl)piperidin-4-yl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(1-pyridin-2-ylpiperidin-4-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(1-pyridazin-3-ylpiperidin-4-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[2-(pyridin-3-yloxy)ethyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(5-fluoropyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(5-chloropyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

4-({4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}carbonyl)benzonitrile

2-*tert*-butyl-4-{[1-(3,4-difluorobenzoyl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(1-acetylpiperidin-4-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

3-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

2-*tert*-butyl-5-phenyl-4-({2-[2-(trifluoromethoxy)phenyl]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

4-[(1-benzylpyrrolidin-3-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-yl}amino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N^1-benzyl-N^2-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinamide

2-*tert*-butyl-4-[(1-isobutyrylpiperidin-4-yl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-tert-butyl-5-phenyl-4-[(2-pyridin-2-ylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[2-(2-chlorophenyl)ethyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[1-(2-phenylethyl)piperidin-4-yl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(4-{[4-(trifluoromethyl)phenyl]thio}cyclohexyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2-{[3-(trifluoromethoxy)phenyl]thio}ethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[2-(4-chlorophenoxy)ethyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({2-[3-(trifluoromethoxy)phenoxy]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

tert-butyl 3-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}azetidine-1-carboxylate

2-*tert*-butyl-4-[(2,2-dimethylpropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-(*tert*-butylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl ({[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetyl}amino)acetate

2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(1-methylpiperidin-4-yl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2-hydroxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(biphenyl-2-ylthio)ethyl]amino}-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[2-(pyrrolidin-3-ylthio)ethyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[(5-methyl-3-phenylisoxazol-4-yl)methyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({2-[4-(trifluoromethoxy)phenyl]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2,2,2-trifluoroethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,3-dihydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propanenitrile

4-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(3-chloro-4-methoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-isobutyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

2-isopropyl-5-phenyl-4-[(1-pyridin-2-ylpiperidin-4-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

4-(2-{[2-(4-fluorobenzyl)-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl]amino}ethyl)phenyl methanesulfonate

2-isopropyl-4-(isopropylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(1-pyridin-2-ylazetidin-3-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[(5-methylisoxazol-3-yl)methyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(2-aminopyridin-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(2-pyridin-4-ylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(2-pyridin-3-ylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(3,5-dimethylisoxazol-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[2-({2-[(5-methylisoxazol-3-yl)methyl]-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl}amino)ethyl]phenyl methanesulfonate

4-{[2-(3,5-dimethyl-1*H*-pyrazol-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

4-[2-({2-[(methylthio)methyl]-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl}amino)ethyl]phenyl methanesulfonate

2,6-Dimethylphenyl 4-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]butanoate

2-Mesitylethyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

2-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl (2,6-dimethylphenyl)acetate

Phenyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

4-(Trifluoromethoxy)phenyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

1-Methylpiperidin-4-yl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

2-Mesityl-1-methylethyl [(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetate

4-Methoxybenzyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

4-Methoxyphenyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, there is provided a compound of formula (I) in which R^1 is selected from ethyl, isopropyl, n-butyl, *tert*butyl, cyclopentyl, hexyl, benzyl, 2-methoxyethyl, pyridin-2ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, tetrahydrofuran-2-ylmethyl or 2-(3-fluorophenyl)ethyl;

R^2 is phenyl; and

R^3 is selected from n-butyl, n-hexyl, benzyl, 3-[3-(hydroxymethyl)phenoxy]propyl, 4-phenylbutyl, 3-(2-methoxyphenoxy)propyl, 3-[4-(hydroxymethyl)phenoxy]propyl, 3-(2-fluorophenoxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(pyridin-3-yloxy)propyl, 3-(pyridin-4-yloxy)propyl, 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 3-(phenylthio)propyl, 3-phenoxypropyl, 3-(3-chlorophenoxy)propyl, 3-(3-fluorophenoxy)propyl, 3-(4-fluorophenoxy)propyl, 1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl, *cis*-4-hydroxycyclohexyl, 4-phenoxybutyl, 3-[(1-oxidopyridin-3-yl)oxy]propyl, 3-(4-methoxyphenoxy)propyl, 4,4-difluorocyclohexyl, 2-phenoxyethyl, 2-phenylethyl, 4-(difluoromethoxy)benzyl, *trans*-4-hydroxycyclohexyl, 3-hydroxypropyl, 2,3-dihydro-1,4-benzodioxin-2-ylmethyl, 4-hydroxycyclohexyl, 3-(4-chlorophenoxy)propyl, 1,3-benzodioxol-5-ylmethyl, 2,3-dihydro-1*H*-inden-2-yl, 2-(morpholin-4-yl)ethyl, 3-(4-isopropylphenoxy)propyl, 3-[benzyl(butyl)amino]propyl, 3-(3,5-dipropoxyphenoxy)propyl, 2,2-diphenylethyl, 2-(1*H*-imidazol-4-yl)ethyl, 4-morpholin-4-ylbenzyl, 3-(2-methoxyethoxy)propyl, 3-morpholin-4-ylpropyl, 2-methoxyethyl, tetrahydro-2*H*-pyran-4-yl, 4-hydroxycyclohexyl, 4-methoxybenzyl, 3-(3-hydroxyphenoxy)propyl, 3-(3-acetamidophenoxy)propyl, 3-(4- *N,N*-dimethylaminocarbonylmethylphenoxy)propyl, 3-(3-carboxymethylphenoxy)propyl, 3-(3-methoxycarbonylmethylphenoxy)propyl, 3-(3-methoxycarbonylphenoxy)propyl, 3-(4-carboxymethylphenoxy)propyl, 3-(4-methoxycarbonylmethylphenoxy)propyl, 3-(3-acetylaminophenoxy)propyl, 3-(4-hydroxyphenylcarboxy)propyl, 3-(4-carboxyphenoxy)propyl, 1-(2-nitriloethyl)piperidin-4-yl, isopropyl, ethyl; 2,2-dimethylpropyl, *tert*butyl, 2-(2-methoxyethoxy)ethyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, methyl ethanoylglycinate, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, 1,3,5-trimethyl-1H-pyrazol-4-ylmethyl, 3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl, 2-(pyrrolidin-3-ylthio)ethyl, 2-[1-(*tert*butoxycarbonyl)pyrrolidin-3-yl]ethyl, 2-[1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]ethyl, 2-{[1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]thio}ethyl, 2-pyridin-2-ylethyl, 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl, 2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl, 3-(pyridin-2-yloxy)propyl, 1-(*tert*-butoxycarbonyl)piperidin-4-yl, 1-acetylpiperidin-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-isobutyrylpiperidin-4-yl, 1-pyridin-2-ylpiperidin-4-yl, 1-(5-fluoropyridin-2-yl)piperidin-4-yl, 1-(5-chloropyridin-2-yl)piperidin-4-yl, 1-(5-methylpyridin-2-yl)piperidin-4-yl, 1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 1-(6-chloropyridin-3-yl)piperidin-4-yl, 1-pyridazin-3-ylpiperidin- chlorophenyl)ethyl, 3-(3-

carboxyphenoxy)propyl, 3-[3-(2-methoxy-2-oxoethyl)phenoxy]propyl, 3-[4-(2-methoxy-2-oxoethyl)phenoxy]propyl, , 3-{4-[2-(dimethylamino)-2-oxoethyl]phenoxy}propyl, 3-[(4-hydroxybenzoyl)oxy]propyl, 2-{2-[(methylsulfonyl)oxy]phenoxy}ethyl, 2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl, 2-[2-(methoxycarbonyl)phenoxy]ethyl, 2-(4-chlorophenoxy)ethyl, 2-[3-(trifluoromethoxy)phenoxy]ethyl, 2-{[3-(trifluoromethoxy)phenyl]thio}ethyl, 2-(benzylamino)-2-oxoethyl, 2-{[3-(difluoromethoxy)benzyl]amino}-2-oxoethyl.4-yl, 1-(6-chloropyridazin-3-yl)piperidin-4-yl, 1-(6-methoxypyridazin-3-yl)piperidin-4-yl, 1-(4-cyanobenzyl)piperidin-4-yl, 1-[2-(trifluoromethyl)benzoyl]piperidin-4-yl, 1-[3-(methoxycarbonyl)benzyl]piperidin-4-yl, 1-benzylpiperidin-4-yl, 1-benzoylpiperidin-4-yl, 1-(phenylacetyl)piperidin-4-yl, 1-(4-cyanobenzoyl)piperidin-4-yl, 1-(3,4-difluorobenzoyl)piperidin-4-yl, 1-(2-phenylethyl)piperidin-4-yl, 1-(2-phenylethyl)piperidin-4-yl, 1-benzylpyrrolidin-3-yl, 4-{[4-(trifluoromethyl)phenyl]thio}cyclohexyl, 1-[(5-methylisoxazol-3-yl)methyl]piperidin-4-yl, 1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl, 1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl, 2-{4-[(methylsulfonyl)oxy]phenyl}ethyl, 2-[4-(aminosulfonyl)phenyl]ethyl, 2-(4-cyanophenyl)ethyl, 2-(3-cyanophenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl or 2-[3-(trifluoromethoxy)phenyl]ethyl.

According to a further aspect of the invention R^1 and R^3 are the same as for any of the embodiments 1 to 16, and R^2 is unsubstituted phenyl.

According to a further aspect of the invention R^1 and R^3 are the same as for any claims, aspects or embodiments hereinbefore or hereinafter, and R^2 is unsubstituted phenyl.

According to a further aspect of the invention R^1 and R^2 are the same as for the first embodiment of the invention, and R^3 is the same as for the first embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the first embodiment of the invention, and R^3 is the same as for the first embodiment of the invention

except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

According to a further aspect of the invention R^1 and R^2 are the same as for the second embodiment of the invention, and R^3 is the same as for the second embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the second embodiment of the invention, and R^3 is the same as for the second embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the third embodiment of the invention, and R^3 is the same as for the third embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the third embodiment of the invention, and R^3 is the same as for the third embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the fourth embodiment of the invention, and R^3 is the same as for the fourth embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the fourth embodiment of the invention, and R^3 is the same as for the fourth embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ,Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl or

C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,.

According to a further aspect of the invention R^1 and R^2 are the same as for the sixth embodiment of the invention, and R^3 is the same as for the sixth embodiment of the invention except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 and R^2 are the same as for the seventh embodiment of the invention, and R^3 is the same as for the seventh embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to one aspect of the invention R^1 and R^2 are the same as for the seventh embodiment of the invention, and R^3 is the same as for the seventh embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

According to a further aspect of the invention R^1 and R^2 are the same as for the 9th embodiment of the invention, and R^3 is the same as for the 9th embodiment of the invention s except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to a further aspect of the invention R^1 and R^2 are the same as for the 10th embodiment of the invention, and R^3 is the same as for the 10th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the 10th embodiment of the invention, and R^3 is the same as for the 10th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the 12th embodiment of the invention, and R^3 is the same as for the 12th embodiment of the invention except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to a further aspect of the invention R^1 and R^2 are the same as for the 13th embodiment of the invention, and R^3 is the same as for the 13th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the 13th embodiment of the invention, and R^3 is the same as for the 13th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the 15th embodiment of the invention, and R^3 is the same as for the 15th embodiment of the invention except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to a further aspect of the invention R^1 and R^2 are the same as for the 16th embodiment of the invention, and R^3 is the same as for the 16th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the 16th embodiment of the invention, and R^3 is the same as for the 16th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 is the same as for the first embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the first embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to one aspect of the invention R^1 is the same as for the second embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the second embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 is the same as for the third embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the third embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to one aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the fourth embodiment of the invention except that MP is excluded; Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 orHet^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 is the same as for the sixth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the sixth embodiment of the invention except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 is the same as for the seventh embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the seventh embodiment of the

invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 is the same as for the 9th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 9th embodiment of the invention except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 is the same as for the 10th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for for the 10th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 is the same as for the 12th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 12th embodiment of the invention except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 is the same as for the 13th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 13th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 is the same as for the 15th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 15th embodiment of the invention except that MP is excluded; and Het^3, A and Het^5 are not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 is the same as for the 16th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 16th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1, Het^1Z, R or Het^2Z.

According to a further aspect of the invention R^1 and R^2 are the same as for the first embodiment of the invention, and R^3 is the same as for the first embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to a further aspect of the invention R^1 and R^2 are the same as for the first embodiment of the invention, and R^3 is the same as for the first embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

According to one aspect of the invention R^1 and R^2 are the same as for the second embodiment of the invention, and R^3 is the same as for the second embodiment of the invention except that MP is excluded, Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 and R^2 are the same as for the second embodiment of the invention, and R^3 is the same as for the second embodiment of the invention except that MP is excluded, Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the third embodiment of the invention, and R^3 is the same as for the third embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to a further aspect of the invention R^1 and R^2 are the same as for the third embodiment of the invention, and R^3 is the same as for the third embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following

independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to one aspect of the invention R^1 and R^2 are the same as for the fourth embodiment of the invention, and R^3 is the same as for the fourth embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 and R^2 are the same as for the fourth embodiment of the invention, and R^3 is the same as for the fourth embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the sixth embodiment of the invention, and R^3 is the same as for the sixth embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; and Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 and R^2 are the same as for the seventh embodiment of the invention, and R^3 is the same as for the seventh embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 and R^2 are the same as for the seventh embodiment of the invention, and R^3 is the same as for the seventh embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

According to a further aspect of the invention R^1 and R^2 are the same as for the 9th embodiment of the invention, and R^3 is the same as for for the 9th embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; and Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 and R^2 are the same as for the 10th embodiment of the invention, and R^3 is the same as for the 10th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 and R^2 are the same as for the 10th embodiment of the invention, and R^3 is the same as for the 10th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b,

$SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the 12th embodiment of the invention, and R^3 is the same as for the 12th embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; and Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 and R^2 are the same as for the 13th embodiment of the invention, and R^3 is the same as for for the 13th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 and R^2 are the same as for the 13th embodiment of the invention, and R^3 is the same as for for the 13th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 and R^2 are the same as for the 15th embodiment of the invention, and R^3 is the same as for the 15th embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; and Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T.

According to one aspect of the invention R^1 and R^2 are the same as for the 16th embodiment of the invention, and R^3 is the same as for the 16th embodiment of the invention except that E is

not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 and R^2 are the same as for the 16th embodiment of the invention, and R^3 is the same as for the 16th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

According to a further aspect of the invention R^1 is the same as for the first embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the first embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; and E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 is the same as for the second embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the second embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; and E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to a further aspect of the invention R^1 is the same as for the third embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the third embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T;

and E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to one aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the fourth embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 or Het^2T; and E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to a further aspect of the invention R^1 is the same as for the sixth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the sixth embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 orHet^2T.

According to one aspect of the invention R^1 is the same as for the seventh embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the seventh embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to a further aspect of the invention R^1 is the same as for the 9th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 9th embodiment of the invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 orHet^2T.

According to one aspect of the invention R^1 is the same as for the 10th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 10th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to a further aspect of the invention R^1 is the same as for the 12th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 12th embodiment of the

invention except that MP is excluded; Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 orHet^2T.

According to one aspect of the invention R^1 is the same as for the 13th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 13th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to a further aspect of the invention R^1 is the same as for the 15th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 15th embodiment of the invention except that MP is excluded; and Het^5 is not substituted by Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T; Het^3 and A are not substituted by Q, QT, Het^1, Het^1T, RT, Het^2 orHet^2T.

According to a further aspect of the invention R^1 is the same as for the 16th embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is the same as for the 16th embodiment of the invention except that E is not substituted by Q, QZ, Het^1, Het^1Z, R, Het^2 or Het^2Z; and Het^4 is not substituted by Q, QZ, Het^1 or R.

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 represents X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 represents Het^3P wherein Het^3 optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more

of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein Het^3 optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 represents AP wherein A optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 represents Het^5P wherein Het^5 optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 represents E which is optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$.

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 is Het^4 which is optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and Het^4 optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention, R^2 is unsubstituted phenyl, and R^3 represents Het^4 which is optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Het^2, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and Het^4 optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Het^2, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

According to an alternative aspect of the invention R^1 is the same as for the fourth embodiment of the invention. R^2 is unsubstituted phenyl, and R^3 represents Het^4 which is optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, RZ, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and Het^4 optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$,

$NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, RZ, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

All of the preceding aspects may also be used with any claims, aspects or embodiments of the invention hereinbefore or hereinafter.

According to an alternative aspect of the invention R^1 is selected from n-butyl, *tert*-butyl or 2-methoxyethyl, R^2 is unsubstituted phenyl, and R^3 is selected from ethyl, 2,2,2-trifluoroethyl, isopropyl, *tert*-butyl, 2,2-dimethylpropyl, n-hexyl, 2-hydroxyethyl, 2-methoxyethyl, 3-hydroxypropyl, 2-(2-methoxyethoxy)ethyl, 3-(2-methoxyethoxy)propyl, methyl ethanoylglycinate or 2,3-dihydroxypropyl.

According to an alternative aspect of the invention R^1 is selected from n-butyl, *tert*-butyl, ethyl, 2-methoxyethyl, R^2 is unsubstituted phenyl, and R^3 is selected from 2,3-dihydro-1,4-benzodioxin-2-ylmethyl, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, , 2-morpholin-4-ylethyl, 2-[1-(*tert*-butoxycarbonyl)azetidin-3-yl]ethyl, 3-morpholin-4-ylpropyl, 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)propyl, 2-(pyrrolidin-3-ylthio)ethyl, 2-{[1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]thio}ethyl or 3-[(1-methylpiperidin-4-yl)oxy]-3-oxopropyl.

According to an alternative aspect of the invention R^1 is selected from ethyl, *tert*-butyl, n-butyl, isopropyl, 2-methoxyethyl, (3-fluorophenyl)ethyl, cyclopentyl, benzyl, pyridin-2ylmethyl, pyridin-3ylmethyl, pyridin-4ylmethyl, tetrahydrofuran-2ylmethyl. isobutyl, 4-fluorobenzyl, (5-methylisoxazol-3-yl)methyl or (methylthio)methyl, R^2 is unsubstituted phenyl, and R^3 is selected from 4-(difluoromethoxy)benzyl, 4-methoxybenzyl, 2,2-diphenylethyl, 2-phenylethyl, 2-{4-[(methylsulfonyl)oxy]phenyl}ethyl, 2-[4-(aminosulfonyl)phenyl]ethyl, 2-(4-cyanophenyl)ethyl, 2-(3-cyanophenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2-[3-(trifluoromethoxy)phenyl]ethyl, 2-(2-chlorophenyl)ethyl, 3-[benzyl(butyl)amino]propyl, 4-phenylbutyl, 3-phenoxypropyl, 3-(2-fluorophenoxy)propyl, 3-(3-fluorophenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(3-chlorophenoxy)propyl, 3-(4-chlorophenoxy)propyl, 3-(2-

methoxyphenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(4-methoxyphenoxy)propyl, 3-(3-carboxyphenoxy)propyl, 3-(4-carboxyphenoxy)propyl, 3-(3-hydroxyphenoxy)propyl, 3-[3-(hydroxymethyl)phenoxy]propyl, 3-[4-(hydroxymethyl)phenoxy]propyl, 3-[3-(2-methoxy-2-oxoethyl)phenoxy]propyl, 3-[4-(2-methoxy-2-oxoethyl)phenoxy]propyl, 3-[3-(acetylamino)phenoxy]propyl, 3-[3-(carboxymethyl)phenoxy]propyl, 3-[3-(methoxycarbonyl)phenoxy]propyl, 3-(4-isopropylphenoxy)propyl, 3-[(1-oxidopyridin-3-yl)oxy]propyl, 3-{4-[2-(dimethylamino)-2-oxoethyl]phenoxy}propyl, 3-[(4-hydroxybenzoyl)oxy]propyl, 2-phenoxyethyl, 2-{2-[(methylsulfonyl)oxy]phenoxy}ethyl, 2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl, 2-[2-(methoxycarbonyl)phenoxy]ethyl, 2-(4-chlorophenoxy)ethyl, 2-[3-(trifluoromethoxy)phenoxy]ethyl, 4-phenoxybutyl, 2-{[3-(trifluoromethoxy)phenyl]thio}ethyl, 3-(phenylthio)propyl, 2-(benzylamino)-2-oxoethyl, 2-{[3-(difluoromethoxy)benzyl]amino}-2-oxoethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(3-chloro-4-methoxyphenyl)ethyl, 2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl, 2-(4-methoxyphenoxy)-2-oxoethyl, 2-[(4-methoxybenzyl)oxy]-2-oxoethyl, 2-(2-mesitylethoxy)-2-oxoethyl, 2-(2-mesityl-1-methylethoxy)-2-oxoethyl, 3-oxo-3-phenoxypropyl, 3-oxo-3-[4-(trifluoromethoxy)phenoxy]propyl, 2-{[(2,6-dimethylphenyl)acetyl]oxy}ethyl or 4-(2,6-dimethylphenoxy)-4-oxobutyl.

According to an alternative aspect of the invention R^1 is selected from *tert*-butyl, ethyl or isopropyl, R^2 is unsubstituted phenyl, and R^3 is selected from 2-(1*H*-imidazol-4-yl)ethyl, 2-pyridin-2-ylethyl, 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl, 2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl, 3-(pyridin-2-yloxy)propyl, 3-(pyridin-3-yloxy)propyl, 3-(pyridin-4-yloxy)propyl, (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl, 3-[(1-oxidopyridin-3-yl)oxy]propyl or (5-methylisoxazol-3-yl)methyl, 2-(2-aminopyridin-4-yl)ethyl, 2-pyridin-4-ylethyl, 2-pyridin-3-ylethyl, 2-(3,5-dimethylisoxazol-4-yl)ethyl or 2-(3,5-dimethyl-1*H*-pyrazol-4-yl)ethyl.

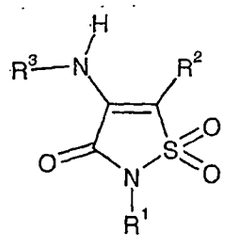
According to an alternative aspect of the invention R^1 is selected from n-butyl, isopropyl or 2-methoxymethyl, R^2 is unsubstituted phenyl, and R^3 is selected from *trans*-4-hydroxycyclohexyl, *cis*-4-hydroxycyclohexyl, 4-hydroxycyclohexyl, 4,4-difluorocyclohexyl or 2,3-dihydro-1*H*-inden-2-yl.

According to an alternative aspect of the invention R^1 is selected from *tert*-butyl, isopropyl or 2-methoxyethyl, R^2 is unsubstituted phenyl, and R^3 is selected from 1-(2-cyanoethyl)piperidin-4-yl, 1-(*tert*-butoxycarbonyl)piperidin-4-yl, 1-acetylpiperidin-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-isobutyrylpiperidin-4-yl or tetrahydro-2*H*-pyran-4-yl.

According to an alternative aspect of the invention R^1 is selected from isopropyl or *tert*-butyl, R^2 is unsubstituted phenyl, and R^3 is selected from 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 1-pyridin-2-ylpiperidin-4-yl, 1-(5-fluoropyridin-2-yl)piperidin-4-yl, 1-(5-chloropyridin-2-yl)piperidin-4-yl, 1-(5-methylpyridin-2-yl)piperidin-4-yl, 1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 1-(6-chloropyridin-3-yl)piperidin-4-yl, 1-pyridazin-3-ylpiperidin-4-yl, 1-(6-chloropyridazin-3-yl)piperidin-4-yl, 1-(6-methoxypyridazin-3-yl)piperidin-4-yl, 1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl, 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-yl or 1-pyridin-2-ylazetidin-3-yl.

All of the preceding aspects may also be used with any claims, aspects or embodiments of the invention hereinbefore or hereinafter.

In an alternative embodiment there is provided a compound of general formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^3 are as defined in any claim, aspect or embodiment of the invention hereinbefore or hereinafter, and wherein R^2 is unsubstituted phenyl.



formula (I)

In another alternative embodiment there is provided a compound of general formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^3 are as defined in any claim, aspect or embodiment of the invention hereinbefore or hereinafter, and wherein R^2 is phenyl which is optionally substituted in the ortho position by any of the suitable substituents described hereinbefore or hereinafter.

In another alternative embodiment there is provided a compound of general Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^3 are as defined in any claim, aspect or embodiment of the invention hereinbefore or hereinafter, and wherein R^2 is phenyl which is optionally substituted by halogen (F, Cl, Br, I).

The above embodiments may be combined with any other embodiment, aspect or claim of the invention described hereinbefore or hereinafter.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the first embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the second embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or

optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the third embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the fourth embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the fifth embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the seventh embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br); OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the 8th embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the 10th embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted

in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the 11th embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the 13th embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the 14th embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F; R^3 is C_1-C_4alkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which

is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

In an alternative embodiment of the invention there is provided a compound of general formula I wherein R^1, R^2 and R^3 are defined as for the 16th embodiment of the invention, with the proviso that when R^1 is C_1-C_4alkyl which is optionally substituted by one or more of F, R^3 is C_3-C_6cycloalkyl, then R^2 is phenyl which is optionally substituted in the meta and/or para position by halogen (F, Cl, Br, I) and/or optionally substituted in the ortho position by position by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, or $C(O)R^b$.

The above embodiments may be combined with any other embodiment, aspect or claim of the invention described hereinbefore or hereinafter.

In an alternative embodiment of the invention there is provided a compound of general formula (I) wherein R^1, R^2, and R^3 are as defined for any aspect, claim or embodiment hereinbefore or hereinafter, with the proviso that when R^1 is C_1-C_4alkyl optionally substituted by one or more F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is not phenyl substituted in the para position by a C_1alkyl that bears one substitutent selected from : NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ or $NR^aC(O)NR^aR^a$, and one substituent selected from: $C(O)R^b$, $C(O)OR^a$ or $C(O)NR^aR^a$; and R^2 is not phenyl substituted in the para position by a straight or branched C_2-C_4alkyl chain in which the terminal carbon atom (i.e. that carbon not connected to the phenyl) bears one substitutent selected from: NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ or $NR^aC(O)NR^aR^a$, and one substituent selected from: $C(O)R^b$, $C(O)OR^a$ or $C(O)NR^aR^a$; wherein R^a and R^b are as defined for any aspect, claim or embodiment hereinbefore or hereinafter.

In an alternative embodiment of the invention there is provided a compound of general formula (I) wherein R^1, R^2, and R^3 are as defined for any aspect, claim or embodiment hereinbefore or hereinafter, with the proviso that when R^1 is C_1-C_4alkyl optionally substituted by one or more F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is

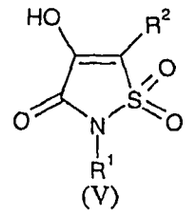
not phenyl substituted in the para position by a C_1alkyl that bears one substitutent selected from : NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ or $NR^aC(O)NR^aR^a$, and one substituent selected from: $C(O)R^b$, $C(O)OR^a$ or $C(O)NR^aR^a$; and R^2 is not phenyl substituted in the para position by a straight or branched C_2-C_4alkyl chain in which the terminal carbon atom (i.e. that carbon not connected to the phenyl) bears one substitutent selected from: NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ or $NR^aC(O)NR^aR^a$, and one substituent selected from: $C(O)R^b$, $C(O)OR^a$ or $C(O)NR^aR^a$; wherein R^a and R^b are as defined for any aspect, claim or embodiment hereinbefore or hereinafter, and R^2 is not phenyl which is further substituted in the ortho or meta positions by H, halogen, C_1-C_4alkyl, OH, OR^b, SR^b, NO_2, CN, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $C(O)OR^a$, NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$ or $NR^aC(O)NR^aR^a$.

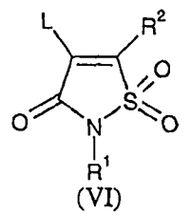
In an alternative embodiment of the invention there is provided a compound of general formula (I) wherein R^1, R^2, and R^3 are as defined for any aspect, claim or embodiment hereinbefore or hereinafter, with the proviso that when R^1 is C_1-C_4alkyl optionally substituted by one or more F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is not phenyl substituted in the meta position by NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $C(O)OR^a$, SO_2NR^aRa, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)OR^a$, $C(O)NR^aR^a$ or $OC(O)R^b$; wherein R^a and R^b are as defined for any aspect, claim or embodiment hereinbefore or hereinafter, with the proviso that when R^2 is phenyl substituted in the meta position by $C(O)OR^a$ then R^a can be H.

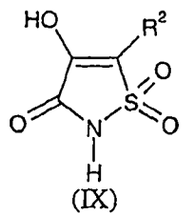
In an alternative embodiment of the invention there is provided a compound of general formula (I) wherein R^1, R^2, and R^3 are as defined for any aspect, claim or embodiment hereinbefore or hereinafter, with the proviso that when R^1 is C_1-C_4alkyl optionally substituted by one or more F, or R^1 is C_3-C_6cycloalkyl; R^3 is C_1-C_4alkyl or C_3-C_6cycloalkyl, then R^2 is not phenyl substituted in one of the meta positions by NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $C(O)OR^a$, SO_2NR^aRa, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)OR^a$, $C(O)NR^aR^a$ or $OC(O)R^b$; wherein R^a and R^b are as defined for any aspect, claim or embodiment hereinbefore or hereinafter, with the proviso that when R^2 is phenyl substituted in the meta position by $C(O)OR^a$ then R^a can be H, and R^2 is not phenyl which is further substituted in the ortho, para or other meta position

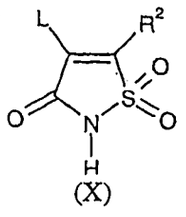
by H, halogen, C_1-C_4alkyl, OH, OR^b, SR^b, NO_2, CN, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $C(O)OR^a$, NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$ or $NR^aC(O)NR^aR^a$.

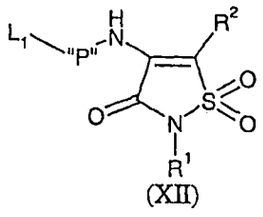
In a further aspect of the invention there is provided a compound of general formula (V), (VI), (IX), (X), (XII) or (XIII)

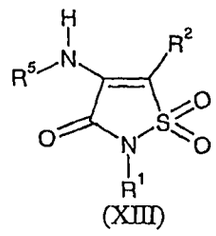

(V)


(VI)


(IX)


(X)


(XII)


(XIII)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is as defined for any aspects, embodiments or claims hereinbefore or hereinafter, R^2 is as defined for any aspects, embodiments or claims hereinbefore or hereinafter, L is a suitable leaving group such as Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, "P" is as defined for P in any aspects, embodiments or claims hereinbefore or hereinafter, L_1 is OH, NH_2, SH or a suitable leaving group such as Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, and R^5 is Het^4 or E wherein Het^4 and E are as defined for any aspects, embodiments or claims hereinbefore or hereinafter, with the proviso that the following compounds are excluded: 4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide, 5-(4-aminophenyl)-4-hydroxy-2-methylisothiazol-3(2*H*)-one 1,1-dioxide, 4-hydroxy-2-methyl-5-(4-nitrophenyl)isothiazol-3(2*H*)-one 1,1-dioxide, 4-hydroxy-2-methyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide, 5-(3,4-dichlorophenyl)-4-hydroxyisothiazol-3(2*H*)-one 1,1-dioxide, 2-benzyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide, and 4-hydroxy-2-(4-methylphenyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide. It shall be understood that protecting groups can be used when L_1 is OH, NH_2 or SH.

Certain compounds of the present invention may exist as tautomers or stereoisomers (e.g. racemate, enantiomer, diastereomer or *E*- or *Z*-isomer). It is to be understood that the present invention encompasses all such tautomers or stereoisomers.

Certain compounds of the present invention may exist as solvates or hydrates. It is to be understood that the present invention encompasses all such solvates or hydrates.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, nitric, methansulphonic, sulphuric, phosphoric, trifluoroacetic, *para*-toluene sulphonic, 2-mesitylen sulphonic, citric, acetic, tartaric, fumaric, lactic, succinic, malic, malonic, maleic, 1,2-ethanedisulphonic, adipic, aspartic, benzenesulphonic, benzoic, ethanesulphonic or nicotinic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention, is, for example, a base-addition salt of a compound of the invention which is sufficiently acidic, for example, a metal salt, for example, sodium, potassium, calcium, magnesium, zinc or aluminum, an ammonium salt, a salt with an organic base which affords a physiologically acceptable cation, which includes quartenery ammonium hydroxides, for example methylamine, ethylamine, diethylamine, trimethylamine, *tert*-butylamine, triethylamine, dibenzylamine, N,N-dibenzylethylamine, cyclohexylethylamine, tris-(2-hydroxyethyl)amine, hydroxyethyl diethylamine, (1R, 2S)-2-hydroxyinden-1-amine, morpholine, N-methylpiperidine, N-ethylpiperidine, piperazine, methylpiperazine, adamantylamine, choline hydroxide, tetrabutylammonium hydroxide, tris-(hydroxymethyl)methylamine hydroxide, L-arginine, N-methyl D-glucamine, lysine or arginine.

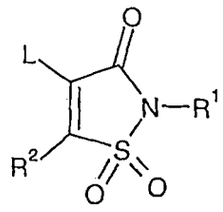
The compound of the formula (I), or other compounds disclosed herein, may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides of a compound of the formula (I).

Methods of preparation

The compounds of the invention may be prepared as outlined in the Schemes below. However, the invention is not limited to these methods. The compounds may also be prepared as described for structurally related compounds in the prior art. The reactions can be carried out according to standard procedures or as described in the experimental section.

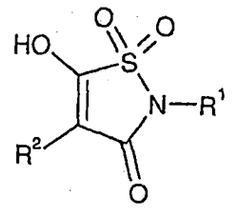
In the Schemes below the term "reagent" means a reagent that can transform a hydroxy group into a leaving group L. Examples of such leaving groups are for instance Cl, Br, I, methanesulfonate (OMs), p-toluensulfonate or trifluoromethanesulfonate (OTf). Furthermore, in all Schemes below R^1, R^2 and R^3 are as defined for any aspects, embodiments or claims hereinbefore or hereinafter.

Schemes I - IX illustrate different processes for synthesizing compounds of formula (I).



(VI)

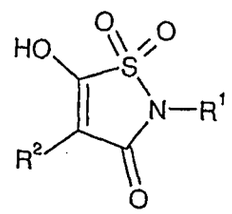
comprising the step of reacting a compound of formula (V)



(V)

with a reagent that can transform the hydroxy group in the compound of formula (V) into a leaving group L, optionally in the presence of an inert organic solvent.

c) A process for the preparation of a compound according to formula (V)



(V)

comprising the step of reacting a compound of formula (IV)

$$R^2CH_2SO_2NHR^1 \quad (IV)$$

with diethyl oxalate, or a suitable equivalent thereof, in the presence of a base such as for instance potassium *tert*-butoxide, optionally in the presence of an inert organic solvent such as THF.

d) A process for the preparation of a compound according to formula (IV)

$$R^2CH_2SO_2NHR^1 \quad (IV),$$

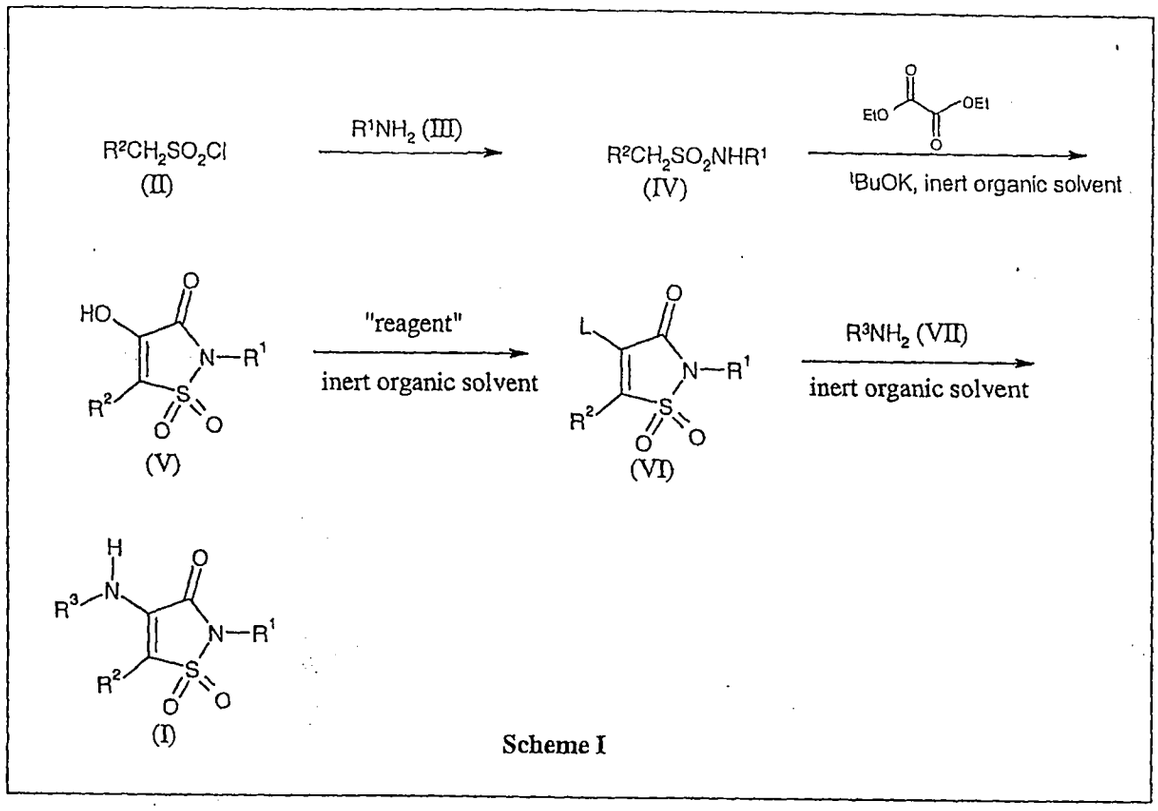
comprising the step of reacting a compound of formula (II)

$$R^2CH_2SO_2Cl \quad (II)$$

with a compound of formula (III)

$$R^1NH_2 \quad (III),$$

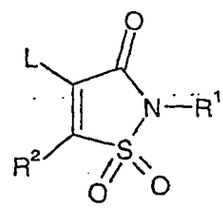
optionally in the presence of a base and an inert organic solvent.



Scheme I

Scheme I describes a method of preparation of compounds according to formula (I), wherein R^1, R^2 and R^3 are as defined for any aspects or embodiments hereinbefore or hereinafter, and L is a leaving group such as for instance Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, comprising the following steps:

a) A process for the preparation of a compound according to formula (I) comprising the step of reacting a compound of formula (VI)



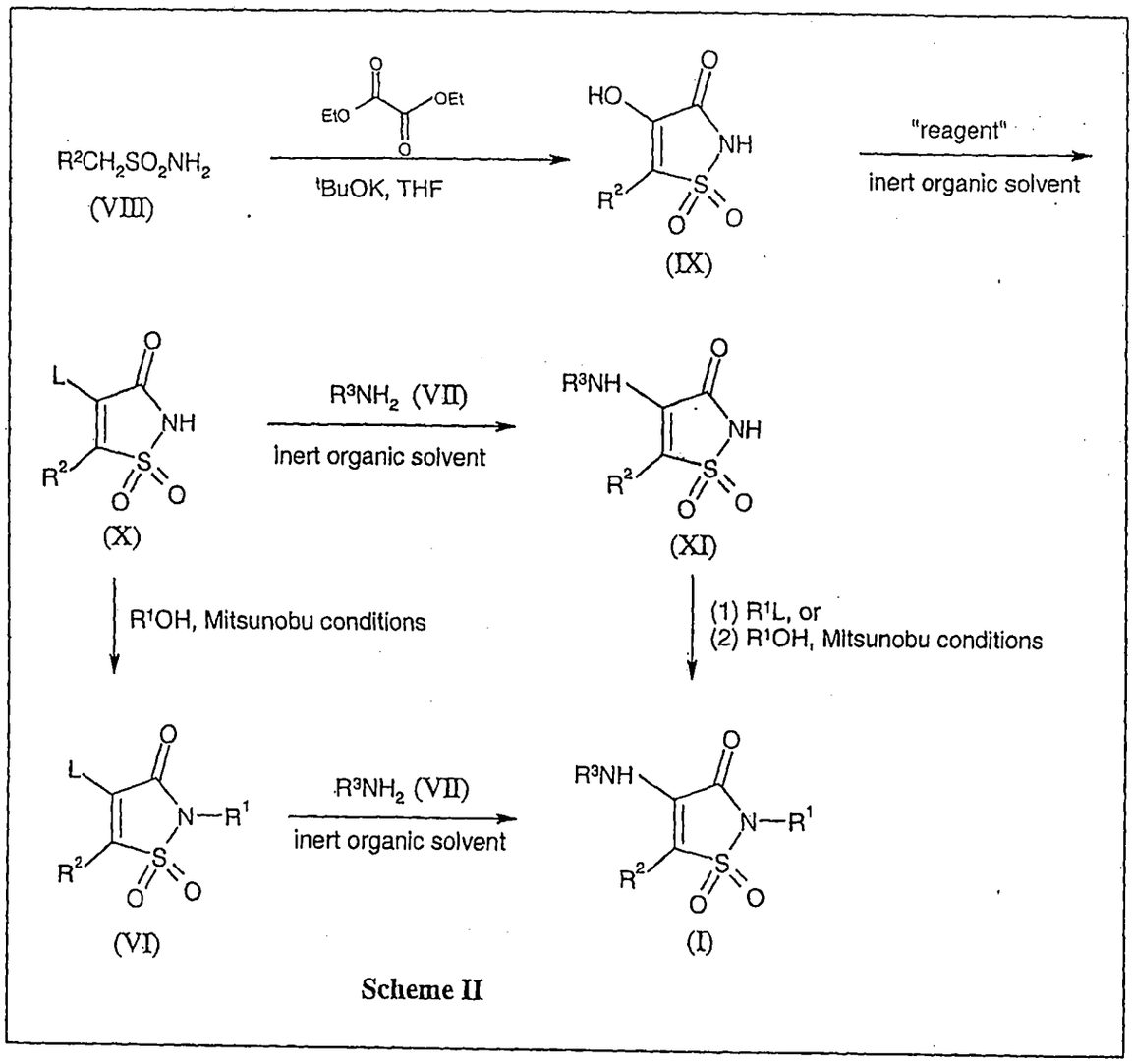
(VI)

with a compound of formula (VII)

R^3NH_2 (VII),

optionally in the presence of an inert organic solvent such as dimethylformamide.

b) A process for the preparation of a compound according to formula (VI)

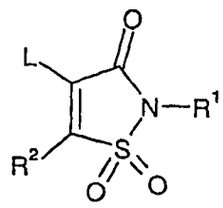


Scheme II

Scheme II describes a method of preparation of compounds according to formula (I), wherein R^1, R^2 and R^3 are as defined for any aspects or embodiments hereinbefore or hereinafter, and L is a leaving group such as for example Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, comprising the following steps:

a) A process for the preparation of a compound according to formula (I) comprising the step of reacting

(i) a compound of formula (VI)



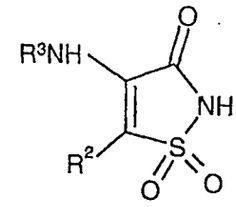
(VI)

with a compound of formula (VII)

R^3NH_2 (VII),

optionally in the presence of an inert organic solvent such as dimethylformamide; or

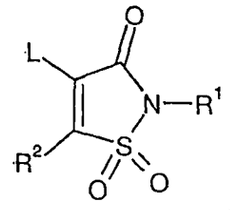
(ii) a compound of formula (XI)



(XI)

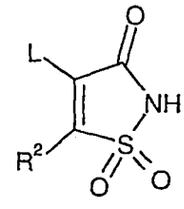
either with R^1OH using Mitsunobu conditions or with an alkylating agent such as R^1L.

b) A process for the preparation of a compound according to formula (VI)



(VI),

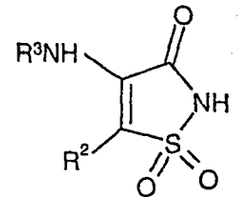
comprising the step of reacting a compound of formula (X)



(X)

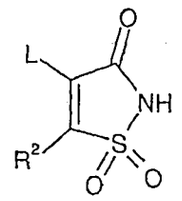
with R^1OH using Mitsunobu conditions.

c) A process for the preparation of a compound according to formula (XI)



(XI)

comprising the step of reacting a compound of formula (X)



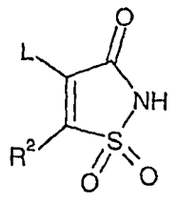
(X)

with a compound of formula (VII)

$$R^3NH_2 \quad (VII),$$

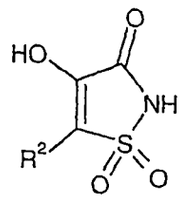
optionally in the presence of an inert organic solvent.

d) A process for the preparation of a compound according to formula (X)



(X)

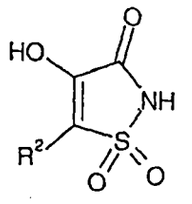
comprising the step of reacting a compound of formula (IX)



(IX)

with a reagent that transforms the hydroxy group in the compound of formula (IX) into a leaving group L.

e) A process for the preparation of a compound of formula (IX)

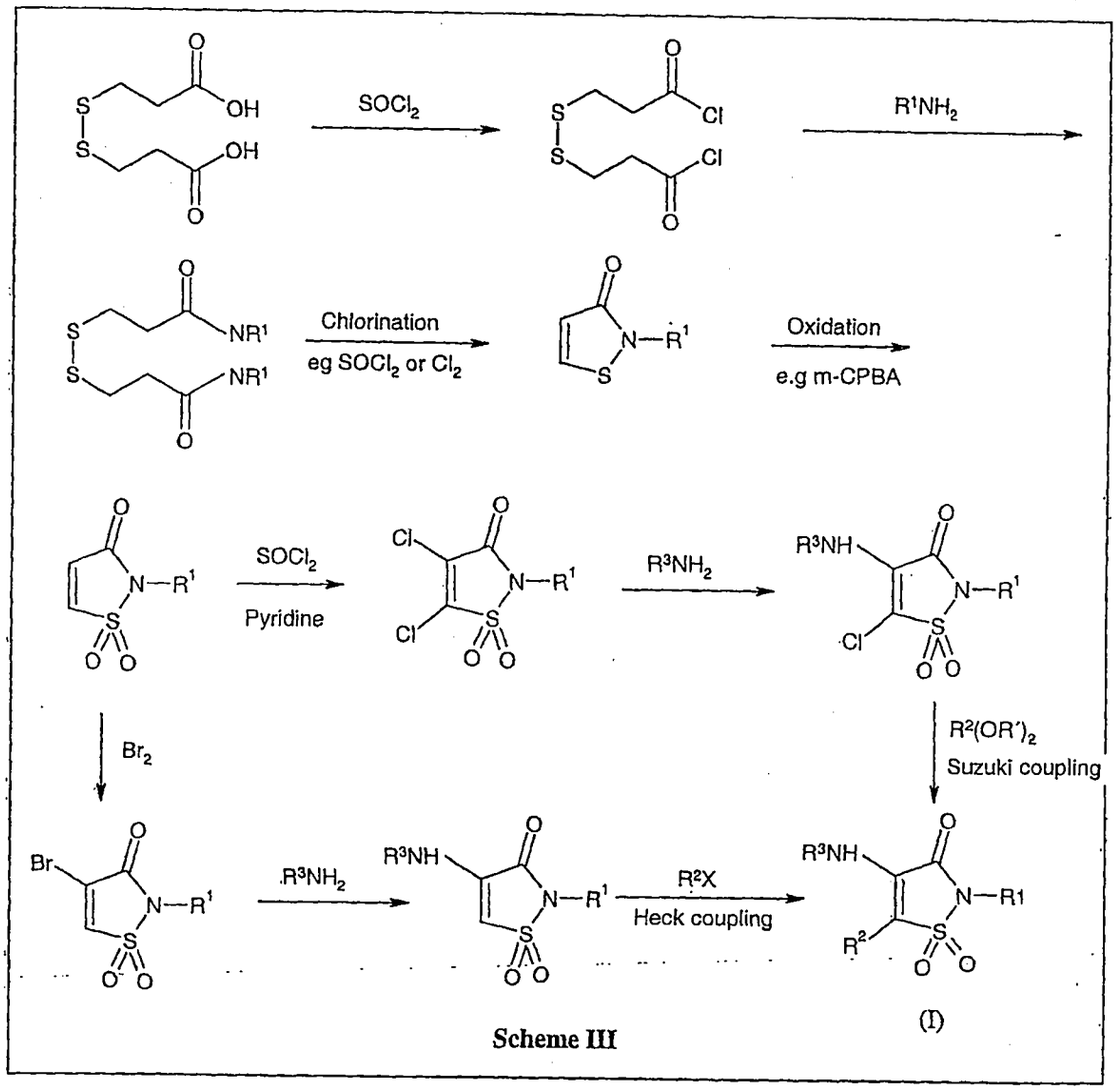


(IX)

comprising the step of reacting a compound of formula (VIII)

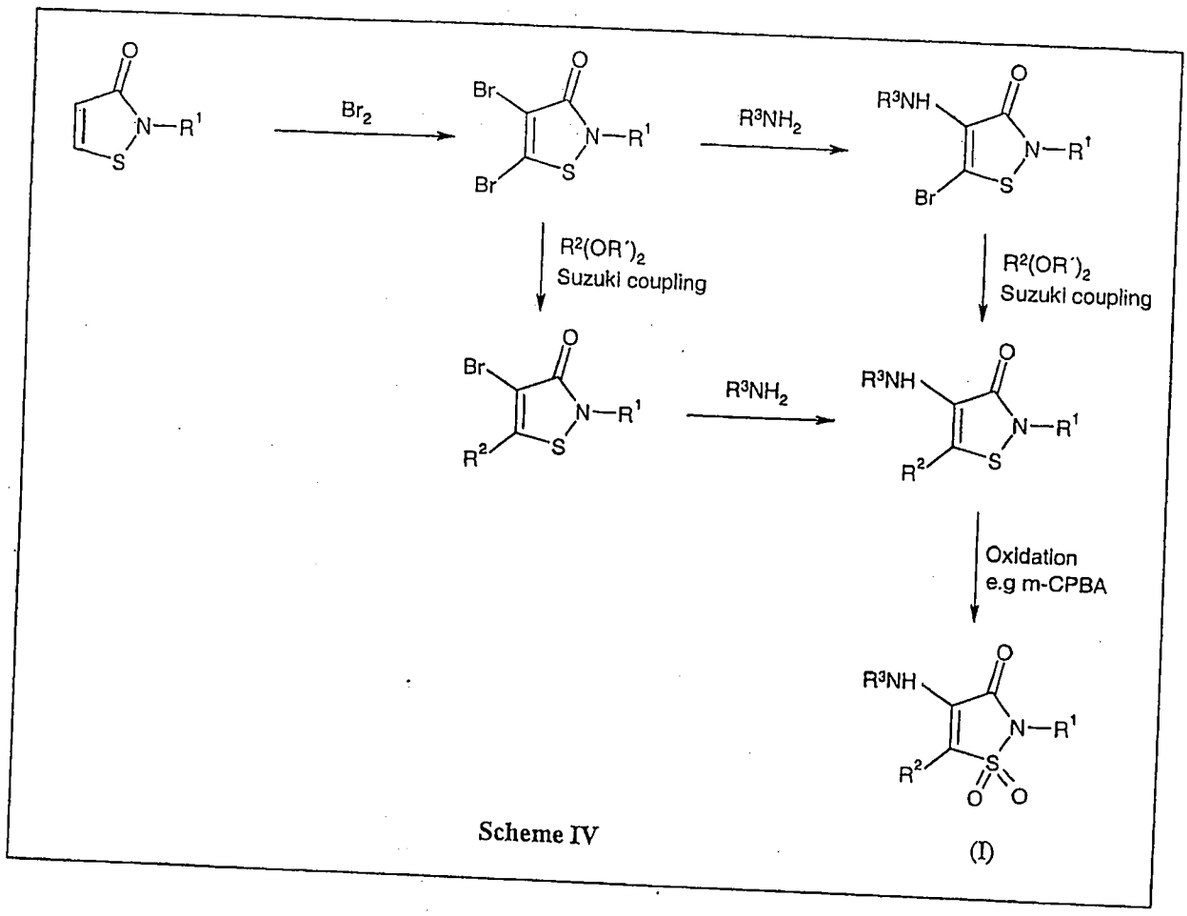
$$R^2CH_2SO_2NH_2 \quad (VIII)$$

with diethyl oxalate, or a suitable equivalent thereof, in the presence of a base such as for instance potassium *tert*-butoxide, optionally in the presence of an inert organic solvent such as THF.



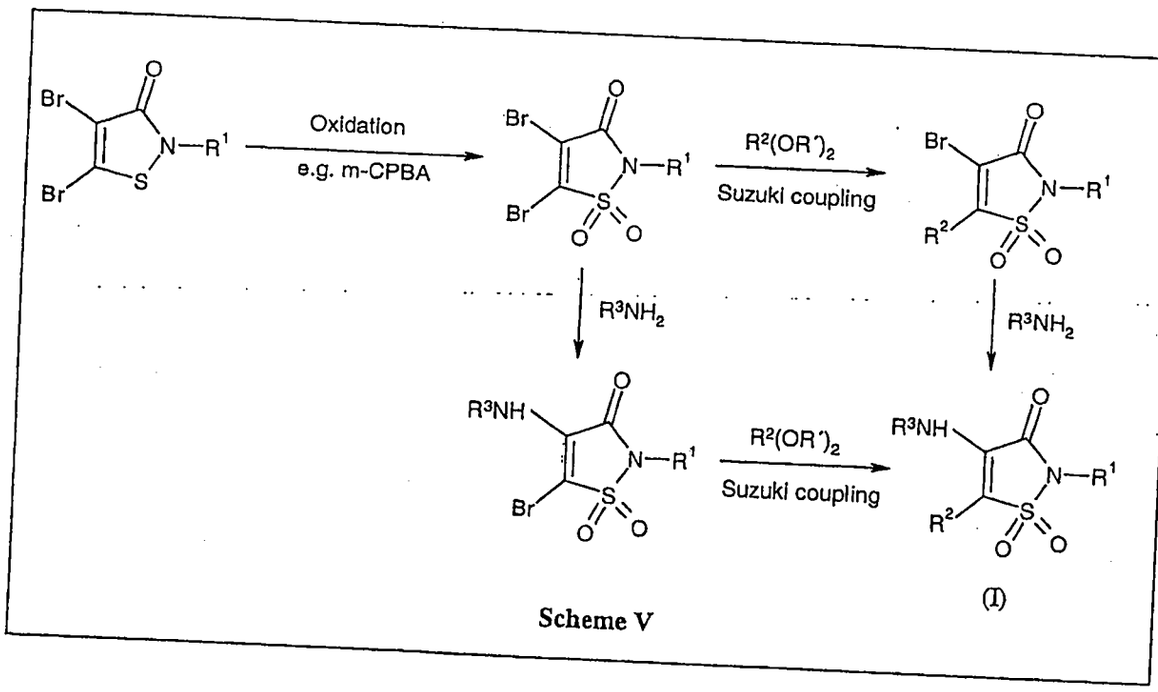
Scheme III

In Scheme III R^2X is an aryl halide, wherein R^2 is defined as for any aspects, embodiments or claims hereinbefore or hereinafter. Furthermore, in Schemes III, IV and V $R^2(OR')_2$ is a reagent wherein R^2 is defined as for any aspects, embodiments or claims hereinbefore or hereinafter and R´ is a hydrocarbon.



Scheme IV

(I)

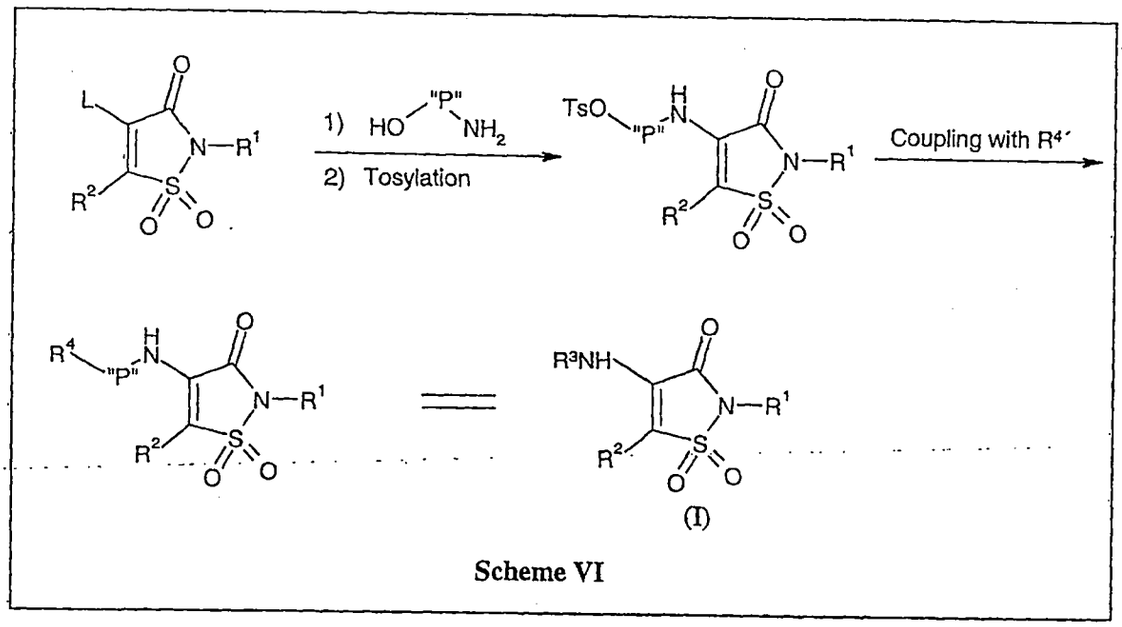


Scheme V

(I)

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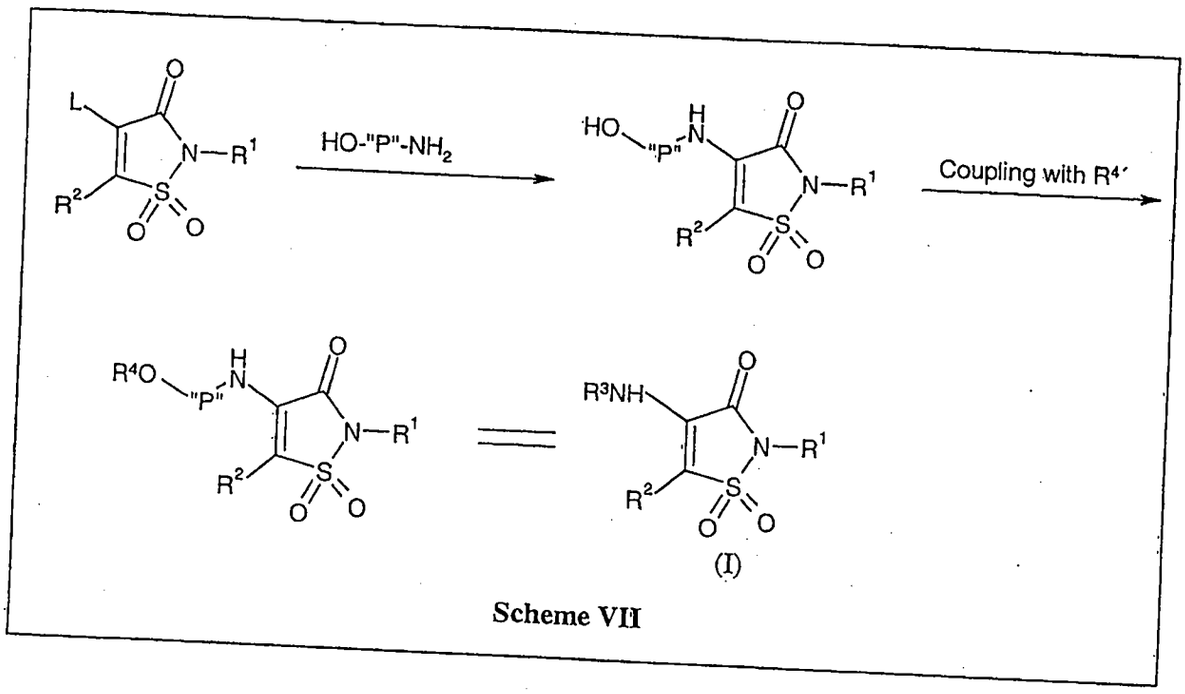
Scheme VI further illustrates the synthesis of some of the compounds of the invention. In Scheme VI "P" is defined as for P in any aspects, embodiments or claims hereinbefore or hereinafter, $R^{4'}$ is a suitable derivative of M, Het^3, A or Het^5, which are optionally substituted by one or more of the following independently selected from: Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T. $R^{4'}$ reacts with the tosylate to yield a compound of formula (I). It is appreciated that in Scheme VI other leaving groups than tosylates may be used. Furthermore, in Scheme VI the tosylate, or another suitable leaving group, can be transformed into a nucleophile such as for instance amino, hydroxy or thio. The coupling with the reagent $R^{4'}$ is performed using appropriate reaction conditions known to a person skilled in the art, and examples of this coupling can be found in the experimental part of this application. R^4-"P"-NH is equal to R^3NH. R^4 is M, Het^3, A or Het^5, which are optionally substituted by one or more of the following independently selected from: Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T. M, Het^3, A, Het^5, Q, T, Het^1, R and Het^2 are defined as for any aspects, embodiments or claims hereinbefore or hereinafter.



Scheme VI

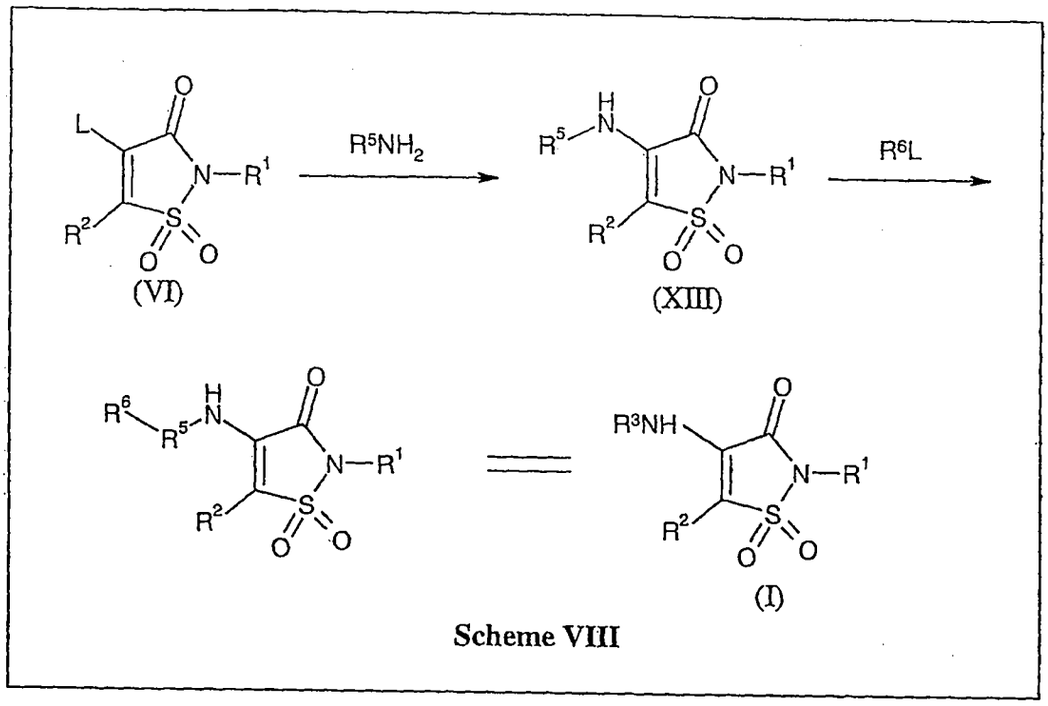
Scheme VII further illustrates the synthesis of some of the compounds of the invention. In Scheme VII "P" is defined as for P in any aspects, embodiments or claims hereinbefore or hereinafter, $R^{4'}$ is a suitable derivative of M, Het^3, A or Het^5, which are optionally substituted by one or more of the following independently selected from: Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T. $R^{4'}$ reacts with the hydroxy group to yield a compound of formula (I). The

coupling with the reagent $R^{4'}$ is performed using appropriate reaction conditions known to a person skilled in the art, and examples of this coupling can be found in the experimental part of this application. R^4O-"P"-NH is equal to R^3NH. R^4 is M, Het^3, A or Het^5, which are optionally substituted by one or more of the following independently selected from: Q, QT, Het^1, Het^1T, R, RT, Het^2 or Het^2T. M, Het^3, A, Het^5, Q, T, Het^1, R and Het^2 are defined as for any aspects, embodiments or claims hereinbefore or hereinafter. It is appreciated that in Scheme VII other nucleophiles than hydroxy may be used such as for instance thio and amino.



Scheme VII

Scheme VIII further illustrates the synthesis of some of the compounds of the invention. In Scheme VIII R^5NH_2 is Het^4NH_2 or E-NH_2. Het^4 and E are as defined for any aspects, embodiments or claims hereinbefore or hereinafter. R^6L is a reagent in which R^6 is Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 or Het^2Z, and L is a leaving group such as for example Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate. Q, Z, Het^1, R, and Het^2 are as defined for any aspects, embodiments or claims hereinbefore or hereinafter. R^6-R^5-NH is equal to R^3NH. The coupling with R^6L is performed using appropriate reaction conditions known to a person skilled in the art, and examples of this coupling can be found in the experimental part of this application.

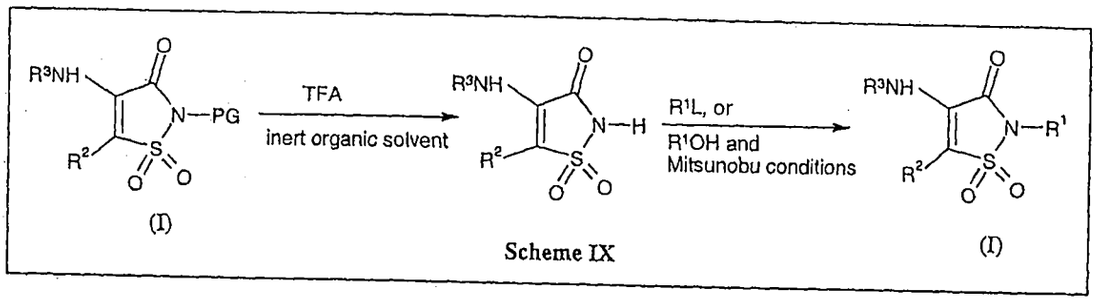


Scheme VIII

The expression "inert organic solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product. Examples of such solvents are for instance dimethylformamide, methylene chloride and acetonitrile.

The individual reactions steps in Schemes I - VIII may be performed while heating either using conventional means such as heating the reaction mixture on an oil bath, or heating the reaction mixture in a microwave oven.

Furthermore, it shall be understood that the R^1 group in a compound of formula (I) can be replaced by another R^1 group, e.g. cyclopentyl. For example, when R^1 is *tert*-butyl it can be removed by deprotection with trifluoroacetic acid, and the resulting compound can subsequently be reacted with an alkylating agent containing the new R^1 group. This is illustrated in Scheme IX, where PG denotes a protecting group.



Scheme IX

It shall be understood that in some of the reactions in this application it may be necessary to use protecting group for functionalities such as for example hydroxyl groups, amino groups, and carboxyl groups. Further representative protecting groups can be found in T. W. Green and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., Wiley and Sons, Inc., New York (1999), which is incorporated hereby by reference in its entirety.

It shall be understood that the diethyl oxalate used in the Schemes above can be exchanged for equivalent reagents such as e.g. methyl oxalyl chloride.

It shall be understood that the potassium *tert*-butoxide used in the Schemes above can be exchanged for equivalent reagents such as e.g. lithium *tert*-butoxide.

Compounds of formula (II) and (IV) are commercially available or may be prepared as described in the experimental part in this patent application or by methods known by those skilled in the art.

Compounds of formula (VII) are commercially available or may be prepared as described in the experimental part in this patent application or by methods known by those skilled in the art. Furthermore, compounds of formula (VII) may be prepared in an analogous way to the procedures described in the experimental part in this patent application.

Certain compounds of formula (V), (VI), (IX), (X), (XII) and (XIII)are believed to be novel and are claimed herein as useful intermediates in the preparation of compounds of formula (I).

All intermediates are commercially available or may be prepared as described in the experimental part in this patent application or by methods known by those skilled in the art. Furthermore, the intermediates may be prepared in an analogous way to the procedures described in the experimental part in this patent application.

It is to be understood that when R^1 or R^3 represent nitrogen oxides in compounds of formula (I) these are prepared from the corresponding amines and an oxidizing agent such as metachloroperbenzoic acid (MCPBA) optionally in the presence of an inert organic solvent such as dichloromethane.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.01-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.007 mg to 700 mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg and 250 mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable excipients, oils which may be glycerides, diluents and/or carriers.

Pharmacological properties

The compounds of formula I are useful for normalization of cholesterol homeostasis, decreasing intestinal cholesterol absorption, improving reverse cholesterol transport, improving HDL functionality, increasing HDL-cholesterol levels, decreasing LDL-cholesterol levels, decreasing cholesterol content of apoB-containing lipoproteins, stimulating cholesterol efflux from vascular cells and/or decreasing the inflammatory response of vascular cells. As a consequence of these properties the compounds of formula I are expected to have anti-atherosclerotic effects.

The compounds of formula I are useful in the prevention or treatment of cardiovascular disease in a mammal, particularly a human. The compounds of formula I are useful in the prevention or treatment of atherosclerosis in a mammal, particularly a human. Cardiovascular disease includes but is not limited to conditions associated with atherosclerosis, arteriosclerosis, hypercholesterolemia, and other kinds of dyslipidemia that increase the risk for cardiovascular disease. In particular the compounds of formula I are useful in the treatment or prevention of cardiovascular disease, especially those involving atherosclerosis, hypercholesterolemia and dyslipidemia.

The compounds of formula I also serve to prevent lipid accumulation in, or remove lipids from, tissue deposits such as atherosclerotic plaques or xanthomas in a patient with atherosclerotic disease manifest by clinical signs such as angina, claudication, bruits, one that has suffered a mycardial infarction, stroke or transient ischemic attack, or one diagnosed by angiography, sonography or MRI.

The compounds of formula I also serve to prevent or reduce the risk of developing atherosclerosis, as well as for halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a prophylactically or therapeutically effective amount, as appropriate, of a compound of formula I to a mammal, including a human, who is at risk of developing atherosclerosis or who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease including restenosis following revascularization procedures, coronary

heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease including multi-infarct dementia, and peripheral vessel disease including erectile dysfunction are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease".

The present compounds of formula I are also useful for the prophylaxis and/or treatment of clinical conditions associated with atherosclerosis such as inherited or induced hypercholesterolemia as well as inherited or induced reduced sensitivity to insulin (insulin resistance syndrome also known as metabolic syndrome) and associated metabolic disorders.These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, type 2 diabetes, type 1 diabetes and other more rare forms of diabetes mellitus and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated VLDL triglyceride rich particles, high ApoB levels, low HDL levels associated with low apoAI levels in the presence of small, dense, LDL particles, phenotype B.

The compounds of formula I are expected to be useful in treating patients with combined or mixed hyperlipidemias and dyslipidemias, especially low HDL levels with or without other manifestations of the metabolic syndrome.

The compounds of formula I are expected to be useful in treating patients with low HDL levels of other reasons than metabolic syndrome or type 2 diabetes.

Treatment with the compounds of formula I are expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency. The insulin sensitizing effect of the compounds of formula I is also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed.

The compounds of formula I may also be useful for the prevention or treatment of inflammation and neurodegenerative diseases or neurological disorders. Accordingly, this invention also provides a method for preventing or treating inflammation in the CNS, reducing amyloid pathology and a method for preventing or treating neurodegenerative diseases or disorders characterized by neuron degeneration, neuron injury or impaired plasticity or inflammation in the CNS. The neurodegenerative diseases or conditions characterized by neuron degeneration and inflammation will include but will not be limited to stroke, Alzheimer's disease, fronto-temporal dementias (taupathies), peripheral neuropathy, Parkinson's disease, dementia with Lewy bodies, Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis.

The compounds of formula I are useful in preventing or treating inflammatory conditions or diseases. These diseases or conditions will include but will not be limited to atherosclerotic diseases such as angina pectoris and myocardial infarction but also rheumatoid arthristis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, degenerative joint disease, one or more connective tissue diseases, ankylosing spondolytis, bursitis, Sjogren´s syndrome, psoriasis, psoriatic arthritis, neuraligia, synovitis, glomerulonephritis, vasculitis or sarcoidosis as well as inflammatory bowel diseases such as Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome and distal proctitis. Compounds of formula I may also be used in other inflammatory conditions of the lung including asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease and pneumonia bronchitis.

Furthermore the compounds of formula I may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity and cancer.

The present invention provides a method of treating and/or preventing rheumatoid arthritis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing juvenile rheumatoid arthritis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing systemic lupus erythematosus comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing osteoarthritis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing degenerative joint disease comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing one or more connective tissue diseases comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing ankylosing spondolytis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing bursitis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing Sjogren´s syndrome comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing psoriasis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing psoriatic arthritis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing neuraligia comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing synovitis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing glomerulonephritis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing vasculitis or sarcoidosis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing Coeliac disease comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing proctitis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing eosinopilic gastro-enteritis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing mastocytosis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing microscopic colitis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing indeterminant colitis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing irritable bowel disorder comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing inflammatory bowel disease comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing Crohn's disease comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing ulcerative colitis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing irritable bowel syndrome comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing cardiovascular disease comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing atherosclerosis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing hypercholesterolemia comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for improving reverse cholesterol transport comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for decreasing intestinal cholesterol absorption comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for increasing HDL-cholesterol levels comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for decreasing LDL-cholesterol levels comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing inflammatory conditions comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing Alzheimer´s disease comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing arteriosclerosis comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing conditions associated with a need for improving HDL function comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing hyperlipidemic conditions comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing dyslipidemic conditions comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating and/or preventing dyslipidemia comprising the administration of an effective amount of a compound of formula (I) to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of formula (I) as a medicament.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of rheumatoid arthritis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of juvenile rheumatoid arthritis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of systemic lupus erythematosus.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of osteoarthritis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of degenerative joint disease.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of one or more connective tissue diseases.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of ankylosing spondolytis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of bursitis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of Sjogren´s syndrome.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of psoriasis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of psoriatic arthritis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of neuraligia.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of synovitis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of glomerulonephritis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of vasculitis or sarcoidosis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of Coeliac disease.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of proctitis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of eosinopilic gastro-enteritis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of mastocytosis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of microscopic colitis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of indeterminant colitis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of irritable bowel disorder.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of inflammatory bowel disease.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of Crohn´s disease.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of ulcerative colitis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of irritable bowel syndrome.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of dyslipidemic conditions.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prohylaxis of insulin resistance and/or metabolic disorders.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of cardiovascular disease.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of atherosclerosis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of hypercholesterolemia.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for improving reverse cholesterol transport.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing intestinal cholesterol absorption.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for increasing HDL-cholesterol levels.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing LDL-cholesterol levels.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of inflammatory conditions.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of Alzheimer´s disease.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of arteriosclerosis.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of type 2 diabetes.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for improving HDL function.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidemic conditions.

In a further aspect the present invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of dyslipidemia.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes, inflammation and obesity. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or apoB:apoA-1 an agent that causes a decrease in circulating levels of LDL-cholesterol or apoB or triglycerides. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to correct carbohydrate metabolism treat complications related to micro-angiopathies.

In another aspect of the present invention, the compund of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with cholesterol biosynthesis inhibitors, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable cholesterol biosynthesis inhibitors include HMG CoA reductase inhibitors, squalene synthesis inhibitors and squalene epoxidase inhibitors. Suitable squalene synthesis inhibitor are squalestatin 1, TAK-475, compounds described in WO2005012284 and a suitable squalene epoxidase inhibitor is NB-598.

In this aspect of the invention, the compund of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administrated in association with an HMG CoA reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitably the HMG CoA reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are selected from the group consisting of atorvastatin, fluvastatin, pitavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly preferred statin is, however, rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A preferable particular statin is rosuvastatin calcium salt.

In the present application, the term "cholesterol biosynthesis inhibitors" also includes chemical modifications of the HMG CoA reductase inhibitors, squalene synthesis inhibitors and squalene epoxidase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

In another aspect of the present invention, the compund of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,, may be administered in association with an inhibitor of the ileal bile acid transport system (IBAT inhibitor), or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182,

WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, WO 03/040124, WO 03/040127, WO03/043992, WO03/061604, WO 04/020421, WO 04/076430, EP 864 582, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595 and EP 624 596 and the contents of these patent applications are incorporated herein by reference.

Further suitable compunds possessing IBAT inhibitory activity have been described in WO 94/24087, WO 98/56757, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 02/08211, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, WO 03/091232, WO 03/106482, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 869 121, EP 1 070 703 and EP 597 107 and the contents of these patent applications are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiazepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β-D-glucopyranosiduronic acid (EP 864 582). A further suitable compound possessing IBAT inhibitory activity is S-8921 (EP 597 107).

In another aspect of the present invention, the compund of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a cholesterol absorption antagonist , or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example AVE-5530 or for example azetidinones such as ezetrol (zetia, ezetimibe) and those described in US 5,767,115 which are incorporated herein by reference. Suitable compounds possessing cholesterol absorption antagonist activity have been described, see for instance the compounds described in WO 02/50027, WO 02/66464, WO 04/005247, WO 04/000803, WO 04/000804, WO 04/000805, WO05021495, WO05021497 and WO05033100 which are incorporated herein by reference.

solvates of such salts or prodrugs thereof, including slow release and combination products, for example, nicotinic acid (niacin), acipimox, nicofuranose, NIASPAN® and niceritrol.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a acyl coenzymA: cholesterol O-acyltransferase (ACAT) inhibitor, or ACAT2 or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example CS-505, eflucimibe (F-12511), K-604 and SMP-797.

In yet another aspect of the invention, the compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with modulators of nuclear hormone receptors such as farnesoid X receptor (FXR), or pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof for example INT-747, or modulators of nuclear receptors such as retenoid X receptor (RXR), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a phytosterol compound, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example stanols and FM-VP4.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a sulfonylurea for example: glimepiride, glibenclamide (glyburide),

gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcylamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an antihypertensive compound for example althiazide, benzthiazide, captopril, carvedilol, chlorothiazide sodium, clonidine hydrochloride, cyclothiazide, delapril hydrochloride, dilevalol hydrochloride, doxazosin mesylate, fosinopril sodium, guanfacine hydrochloride, methyidopa, metoprolol succinate, moexipril hydrochloride, monatepil maleate, pelanserin hydrochloride, phenoxybenzemine hydrochloride, prazosin hydrochloride, primidolol, quinapril hydrochloride, quinaprilat, ramipril, terazosin hydrochloride, candesartan, candesartan cilexetil, telmisartan, amlodipine besylate, amlodipine maleate and bevantolol hydrochloride, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an angiotensin converting enzyme (ACE) inhibitor. Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranopril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril

sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, hemorphin-4, imidapril, indolapril, indolaprilat, lisinopril, lyciumin A, lyciumin B, moexipril, moexiprilat, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors are ramipril and ramiprilat.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, telmisartan and eprosartan. Particularly preferred angiotensin II receptor antagonists or pharmaceutically acceptable derivatives thereof are candesartan and candesartan cilexetil, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an andrenergic blocker. Andrenergic blocker include an alpha andrenergic blocker, or a beta andrenergic blocker, or a mixed alpha/beta andrenergic blocker or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Examples of andrenergic blockers are bretylium tosylate, dihydroergotamine so mesylate, phentolamine mesylate, solypertine tartrate, zolertine hydrochloride, carvedilol, labetalol hydrochloride, fenspiride hydrochloride, labetalol hydrochloride, proroxan, alfuzosin hydrochloride, acebutolol, acebutolol hydrochloride, alprenolol hydrochloride, atenolol, bunolol hydrochloride, carteolol hydrochloride, celiprolol hydrochloride, cetamolol hydrochloride, cicloprolol hydrochloride, dexpropranolol hydrochloride, diacetolol hydrochloride, dilevalol hydrochloride, esmolol hydrochloride, exaprolol hydrochloride, flestolol sulfate, labetalol hydrochloride, levobetaxolol hydrochloride, levobunolol hydrochloride, metalol hydrochloride, metoprolol, metoprolol tartrate, nadolol, pamatolol

sulfate, penbutolol sulfate, practolol, propranolol hydrochloride, sotalol hydrochloride, timolol, timolol maleate, tiprenolol hydrochloride, tolamolol, bisoprolol, bisoprolol fumarate and nebivolol or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an andrenergic stimulant for example combination product of chlorothiazide and methyldopa, the combination product of methyidopa hydrochlorothiazide and methyldopa, clonidine hydrochloride, clonidine, the combination product of chlorthalidone and clonidine hydrochloride and guanfacine hydrochloride, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with calcium channel blocker for example clentiazem maleate, amlodipine besylate, isradipine, nimodipine, felodipine, nilvadipine, nifedipine, teludipine hydrochloride, diltiazem hydrochloride, belfosdil, verapamil hydrochloride or fostedil, or an AT-1 blocker, or a saluretic, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a diuretic for example the combination product of hydrochlorothiazide and spironolactone and the combination product of hydrochlorothiazide and triamterene, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a vasodilator for example coronary vasodilators (for example fostedil, azaclorzine hydrochloride, chromonar hydrochloride, clonitrate, diltiazem hydrochloride, dipyridamole, droprenilamine, erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate, lidoflazine, mioflazine hydrochloride, mixidine, molsidomine, nicorandil,

nifedipine, nisoldipine, nitroglycerine, oxprenolol hydrochloride, pentrinitrol, perhexiline maleate, prenylamine, propatyl nitrate, terodiline hydrochloride, tolamolol and verapamil), or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a anti-anginal agents for example amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butoprozine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, primidolol, ranolazine hydrochoride, tosifen or verapamil hydrochloride or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an anti-coagulants selected from argatroban, bivalirudin, dalteparin sodium, desirudin, dicumarol, Iyapolate sodium, nafamostat mesylate, phenprocoumon, tinzaparin sodium and warfarin sodium or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an antithrombotic agents for example anagrelide hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, fluretofen, ifetroban, ifetroban sodium, lamifiban, lotrafiban hydrochloride, napsagatran, orbofiban acetate, roxifiban acetate, sibrafiban, tinzaparin sodium, trifenagrel, abciximab and zolimomab aritox or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with other agents that act as or deliver a Factor IIa agonist for example 3DP-4815, AZD-0837, melagatran, ximelagatran, ART-123, lepirudin, AVE-5026, bivaluridin, dabigatran etexilate, E-4444, odiparcil, ardeparin sodium, pegmusirudin, LB-30870, dermatan sulfate, argatroban, MCC-977, desirudin, deligoparin sodium, PGX-100, idraparinux sodium,

SR-123781, SSR-182289A, SCH-530348, TRIB50, TGN-167, TGN-255, and compounds described in WO94/29336, WO97/23499 and WO02/44145, which are incorporated hereby by reference.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a fibrinogen receptor antagonists for example roxifiban acetate, fradafiban, orbofiban, lotrafiban hydrochloride, tirofiban, xemilofiban, monoclonal antibody 7E3 and sibrafiban or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a platelet inhibitors for example cilostezol, clopidogrel bisulfate, epoprostenol, epoprostenol sodium, ticlopidine hydrochloride, aspirin, ibuprofen, naproxen, sulindae, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone and piroxicam, dipyridamole or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a platelet aggregation inhibitors for example acadesine, beraprost, beraprost sodium, ciprostene calcium, itezigrel, lifarizine, lotrafiban hydrochloride, orbofiban acetate, oxagrelate, fradafiban, orbofiban, tirofiban and xemilofiban or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a hemorrheologic agents for example pentoxifylline or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in

association with lipoprotein associated coagulation inhibitors; or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a Factor VIIa inhibitor or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a Factor Xa inhibitor or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a low molecular weight heparin for example enoxaparin, nardroparin, dalteparin, certroparin, parnaparin, reviparin and tinzaparin or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an anti-obesity compound, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example a pancreatic lipase inhibitor e.g. orlistat (EP 129,748), ATL-962, GT-389255 or an appetite (satiety) controlling substance for example sibutramine (Meridia®, Reductil®, GB 2,184,122 and US 4,929,629), PYY 3-36 (amylin), APD-356, 1426, Axokine, T-71, a cannabinoid 1 (CB1) antagonist or inverse agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example rimonabant (EP 656354), AVE-1625, CP945598, SR-147778, SLV-319, and as described in WO01/70700, or a Fatty Acid Synthesis (FAS) inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof or a melanin concentrating hormone (MCH) antagonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example 856464 and as described in WO 04/004726.

In another aspect of the invention, the compounds of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administrated in association with an anti-inflammatory agent such as glucocorticoids, non-steroidal anti-inflammatory agents (NSAID) or intestinal anti-inflammatory agents, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable glucocorticoids will include, but will not be limited to betametason, dexametason, methyl prednisolon, prednisolon, prednison, triamcinolon, hydrocortison, cortison and budesonid. Suitable non-steroidal anti-inflammatory agents will include, but will not be limited to indometacin, diclofenac, ibuprofen as well as acetylsalicylic acid. Suitable intestinal anti-inflammatory agents will include, but will not be limited to amino salicylates such as sulfasalazin, mesalazin, olsalazin and balsalazid.

In another aspect of the invention, the compounds of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administrated in association with a cholinesterase inhibitor or an N-methyl-D-aspartate (NMDA) receptor antagonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, such as donepezil, rivastigmin or galantamin or memantin.

Therefore in an additional feature of the invention, there is provided a method of treating and/or preventing metabolic disorders in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in

this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating and/or preventing hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of dyslipidemia in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of the insulin resistance syndrome in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of cardiovascular disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of

the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of atherosclerosis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of hypercholesterolemia in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for improving reverse cholesterol transport in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for decreasing intestinal cholesterol absorption in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in

simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for increasing HDL-cholesterol levels in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for decreasing LDL-cholesterol levels in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of inflammatory conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of Alzheimer´s disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound

of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of arteriosclerosis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for treating and/or preventing conditions associated with a need for improving HDL function in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of rheumatoid arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of juvenile rheumatoid arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a

compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of systemic lupus erythematosus in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of osteoarthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of degenerative joint disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of one or more connective tissue diseases in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a

solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of ankylosing spondolytis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of bursitis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of Sjogren's syndrome in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of psoriasis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the

other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of psoriatic arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of neuraligia in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of synovitis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of glomerulonephritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of

the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of vasculitis or sarcoidosis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of Coeliac disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of proctitis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of eosinopilic gastro-enteritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount

of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of mastocytosis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of microscopic colitis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of indeterminant colitis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of irritable bowel disorder in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of

the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of inflammatory bowel disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of Crohn´s disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of ulcerative colitis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of irritable bowel syndrome in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount

of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In an additional feature of the invention, there is provided a method for the treatment and/or prohylaxis of dyslipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in simultaneous, sequential or separate administration with an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in a first unit dosage form;
b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment and/or prophylaxis of metabolic disorders and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment and/or prophylaxis of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of dyslipidemia in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a

medicament for use in the treatment and/or prophylaxis of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of cardiovascular disease in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of atherosclerosis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of hypercholesterolemia in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for improving reverse cholesterol transport in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for decreasing intestinal cholesterol absorption in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), of such or a pharmaceutically acceptable salt or solvate thereof, or a solvate a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for increasing HDL-cholesterol levels in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for decreasing LDL-cholesterol levels in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of inflammatory conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of Alzheimer´s disease in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of arteriosclerosis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of a conditions associated with a need for improving HDL function in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of rheumatoid arthritis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of juvenile rheumatoid arthritis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a

medicament for use in the treatment and/or prophylaxis of systemic lupus erythematosus in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of osteoarthritis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis degenerative joint disease in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of one or more connective tissue diseases in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of ankylosing spondolytis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of bursitis in a warm-blooded animal, such as man.

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According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a 10 medicament for use in the treatment and/or prophylaxis of Sjogren´s syndrome in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, 15 and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of psoriasis in a warm-blooded animal, such as man.

20 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of psoriatic arthritis in a 25 warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically 30 acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of neuraligia in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of synovitis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of glomerulonephritis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of vasculitis or sarcoidosis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of Coeliac disease in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a

medicament for use in the treatment and/or prophylaxis of proctitis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of eosinopilic gastro-enteritis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of mastocytosis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of microscopic colitis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of indeterminant colitis in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of irritable bowel disorder in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of inflammatory bowel disease in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of Crohn's disease in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of ulcerative colitis in a warm-blooded animal, such as man.

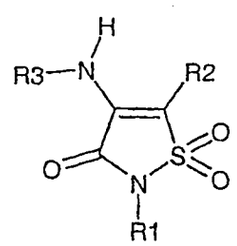
According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of irritable bowel syndrome in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of dyslipidemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Further aspects of the invention

Further aspect 1. A compound of general formula I



or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

cycloalkyl or heterocyclyl each optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

phenyl or heteroaryl each optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

R^2 represents

phenyl which is optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$,

$NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one

or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the folowing: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

and in the above definitions

X represents a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein said alkyl group may optionally be interrupted by O, S, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2;

Y binds to nitrogen in 2-position in the isothiazol-3(2*H*)-one 1,1-dioxide and represents a straight or branched, saturated or unsaturated alkyl group having 1 to 3 carbon atoms wherein said alkyl group may optionally be interrupted or ended by O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c and/or Y is optionally substituted by one or more of the following: OH, F, CN, NR^aR^a, C_1-C_4alkyl, OR^b, SR^b, $S(O)R^b$ or SO_2R^b;

Z binds to E or Het^4 and one of the following: Q, Het^1, R or Het^2, and represents a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein said alkyl group may optionally be interrupted or ended by O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, optionally consists only of one of the following: O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a , SO_2NR^a, NR^aSO_2 and/or Z is optionally substituted by one or more of the following: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $S(O)R^c$, SO_2R^c, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b, OR^b;

M represents a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring composed of 4, 5, 6, 7, 8, 9 or 10 carbon atoms;

E represents a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring composed of 4, 5, 6, 7, 8, 9 or 10 carbon atoms, and the ring binds, unless otherwise specified,

through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide;

A represents an aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or an aromatic bicyclic ring composed of 4, 5, 6, 7, 8, 9 or 10 carbon atoms;

P binds to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide and represents a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein the alkyl group is optionally interrupted or ended by O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 and/or P is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $S(O)R^b$, SO_2R^b, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b or OR^b;

Q represents a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7, 8 carbon atoms, which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

R represents a phenyl group which is optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

T binds to M, Het^3, A or Het^5 and represents an alkyl group having 1 carbon atom or optionally consists of one or more of the following: O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2;

Het^1 represents a saturated or unsaturated non-aromatic 3-10 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon, for example nitrogen, oxygen or sulfur, and wherein the ring optionally is substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$,

$OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

Het^2 represents an aromatic 3-10 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon, for example nitrogen, oxygen and sulfur, and which is substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

Het^3 represents a saturated or unsaturated non-aromatic 3-10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 4-10 membered bicyclic ring in which one or more of the atoms in the monocyclic or bicyclic ring is an element other than carbon, for example nitrogen, oxygen or sulfur;

Het^4 represents a saturated or unsaturated non-aromatic 3-10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 4-10 membered bicyclic ring in which one or more of the atoms in the monocyclic or bicyclic ring is an element other than carbon, for example nitrogen, oxygen or sulfur, and the ring binds, unless otherwise specified, through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide;

Het^5 represents an aromatic 3-10 membered monocyclic ring or an aromatic 4-10 membered bicyclic ring in which one or more of the atoms in the monocyclic or bicyclic ring is an element other than carbon, for example nitrogen, oxygen or sulfur;

R^a independently represents H or a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F;

R^b independently represents a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F; and

R^c independently represents H or a straight or branched, saturated or unsaturated C_1-C_3alkyl chain optionally substituted by one or more F.

Further aspect 2. A compound according to further aspect 1 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

cycloalkyl or heterocyclyl each optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

phenyl or heteroaryl each optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 represents

phenyl which is optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

Further aspect 3. A compound according to further aspect 2 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally

substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

Further aspect 4. A compound according to further aspect 3 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^1 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b or $C(O)R^b$.

Further aspect 5. A compound according to further aspect 1 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

Further aspect 6. A compound according to further aspect 1 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 7. A compound according to further aspect 1 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ; Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the folowing: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 8. A compound according to further aspect 2 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

Further aspect 9. A compound according to further aspect 2 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2,

Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 10. A compound according to further aspect 2 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 11. A compound according to further aspect 3 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

Further aspect 12. A compound according to further aspect 3 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 13. A compound according to further aspect 3 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$,

Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 14. A compound according to further aspect 4 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

X which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

Further aspect 15. A compound according to further aspect 4 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 16. A compound according to further aspect 4 or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

Further aspect 17. A compound according to further aspect 1 in which R^1 is selected from ethyl, isopropyl, n-butyl, *tert*butyl, cyclopentyl, hexyl, benzyl, 2-methoxyethyl, pyridin-2ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, tetrahydrofuran-2-ylmethyl or 2-(3-fluorophenyl)ethyl;

R^2 is phenyl; and

R^3 is selected from butyl, hexyl, benzyl, 3-[3-(hydroxymethyl)phenoxy]propyl, 4-phenylbutyl, 3-(2-methoxyphenoxy)propyl, 3-[4-(hydroxymethyl)phenoxy]propyl, 3-(2-fluorophenoxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(pyridin-3-yloxy)propyl, 3-(pyridin-4-yloxy)propyl, 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 3-(phenylthio)propyl, 3-phenoxypropyl, 3-(3-chlorophenoxy)propyl, 3-(3-fluorophenoxy)propyl, 3-(4-fluorophenoxy)propyl, 1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl, *cis*-4-hydroxycyclohexyl, 4-phenoxybutyl, 3-[(1-oxidopyridin-3-yl)oxy]propyl, 3-(4-methoxyphenoxy)propyl, 4,4-difluorocyclohexyl, 2-phenoxyethyl, 2-phenylethyl, 4-(difluoromethoxy)benzyl, *trans*-4-hydroxycyclohexyl, 3-hydroxypropyl, 2,3-dihydro-1,4-benzodioxin-2-ylmethyl, 4-hydroxycyclohexyl, 3-(4-chlorophenoxy)propyl, 1,3-benzodioxol-5-ylmethyl, 2,3-dihydro-1*H*-inden-2-yl, 2-(morpholin-4-yl)ethyl, 3-(4-isopropylphenoxy)propyl, 3-[benzyl(butyl)amino]propyl, 3-(3,5-dipropoxyphenoxy)propyl, 2,2-diphenylethyl, 2-(1*H*-imidazol-4-yl)ethyl

4-morpholin-4-ylbenzyl, 3-(2-methoxyethoxy)propyl, 3-morpholin-4-ylpropyl, 2-methoxyethyl, tetrahydro-2*H*-pyran-4-yl, 4-hydroxycyclohexyl, 4-methoxybenzyl, 3-(3-hydroxyphenoxy)propyl, 3-(3-acetamidophenoxy)propyl, 3-(4- *N,N*-dimethylaminocarbonylmethylphenoxy)propyl, 3-(3-carboxymethylphenoxy)propyl, 3-(3-methoxycarbonylmethylphenoxy)propyl, 3-(3-methoxycarbonylphenoxy)propyl, 3-(4-carboxymethylphenoxy)propyl, 3-(4-methoxycarbonylmethylphenoxy)propyl, 3-(3-acetylaminophenoxy)propyl, 3-(4-hydroxyphenylcarboxy)propyl, 3-(4-carboxyphenoxy)propyl or 1-(2-nitriloethyl)piperidin-4-yl.

Further aspect 18. A compound selected from one or more of the following:

2-*tert*-butyl-4-({3-[3-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(2-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({3-[4-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N-(3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide

2-*tert*-butyl-4-{[3-(2-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-(4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)-N,N-dimethylacetamide

2-*tert*-butyl-4-{[3-(2-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

(3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-3-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

methyl (3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-4-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-cyclopentyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[3-(phenylthio)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(3-phenoxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl 3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoate

2-benzyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

(4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

2-*tert*-butyl-4-{[3-(3-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl (4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

2-*tert*-butyl-4-{[3-(4-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-({1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

N-(3-{3-[(2-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide

3-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-hydroxybenzoate

4-(benzylamino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-[2-(3-fluorophenyl)ethyl]-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

4-[(cis-4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(4-phenoxybutyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({3-[(1-oxidopyridin-3-yl)oxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-cyclopentyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(4-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(4,4-difluorocyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(tetrahydrofuran-2-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-(hexylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-{[4-(difluoromethoxy)benzyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(trans-4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(3-hydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-3-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-hydroxycyclohexyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

3-{4-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}propanenitrile

2-*tert*-butyl-4-{[3-(4-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-4-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-(2,3-dihydro-1H-inden-2-ylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(2-morpholin-4-ylethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(4-isopropylphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({3-[benzyl(butyl)amino]propyl}amino)-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3,5-dipropoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,2-diphenylethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-ethyl-4-{[2-(1H-imidazol-4-yl)ethyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-morpholin-4-ylbenzyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-{[3-(2-methoxyethoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(3-morpholin-4-ylpropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(2-methoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-(2-methoxyethyl)-5-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide

4-(hexylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(4-hydroxycyclohexyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-methoxybenzyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-2-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

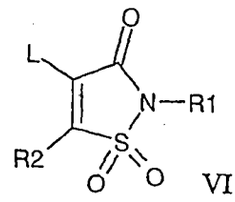
2-*tert*-butyl-4-{[3-(3-hydroxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

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

Further aspect 19. A process for the preparation of a compound according to any one of further aspect 1-18, wherein R^1, R^2 or R^3 are as defined in claim 1, comprising the step of reacting

a compound of formula VI,



VI

wherein R^1 and R^2 are as defined in claim 1 and L is a leaving group such as Cl, Br, I, methanesulfonate or trifluoromethanesulfonate, with a compound of formula VII,

R^3NH_2 VII

wherein R^3 is as defined in claim 1, optionally in the presence of an inert organic solvent such as dimethylformamide.

Further aspect 20. A pharmaceutical formulation comprising a compound according to any one of further aspects 1-18 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Further aspect 21. The use of a compound according to any one of further aspects 1-18 in therapy.

Further aspect 22. The use of a compound according to any of further aspects 1-18 for the manufacture of a medicament for the modulation of the nuclear hormone receptors LXR α and/or β.

Further aspect 23. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of cardiovascular disease.

Further aspect 24. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of atherosclerosis.

Further aspect 25. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of hypercholesterolemia.

Further aspect 26. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for improving reverse cholesterol transport.

Further aspect 27. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing intestinal cholesterol absorption.

Further aspect 28. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for increasing HDL-cholesterol levels.

Further aspect 29. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of conditions associated with a need for decreasing LDL-cholesterol levels.

Further aspect 30. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of inflammatory conditions.

Further aspect 31. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of Alzheimer´s disease.

Further aspect 32. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of arteriosclerosis.

Further aspect 33. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of type 2 diabetes.

Further aspect 34. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament the treatment and/or prophylaxis of conditions associated with a need for improving HDL function.

Further aspect 35. The use of a compound according to any one of further aspects 1-18 in the manufacture of a medicament for the treatment and/or prophylaxis of lipid disorders (dyslipidemia) whether or not associated with insulin resistance.

Further aspect 36. A method of treating and/or preventing lipid disorders (dyslipidemia) whether or not associated with insulin resistance comprising the administration of a compound according to any one of further aspects 1-18 to a mammal in need thereof.

Further aspect 37. A method for treatment and/or prophylaxis of cardiovascular disease comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 38. A method of treating and/or preventing atherosclerosis comprising the administration of an effective amount of a compound of formula I according to any one of further aspects 1-18 to a mammal in need thereof.

Further aspect 39. A method for treatment and/or prophylaxis of hypercholesterolemia comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 40. A method for treatment and/or prophylaxis of conditions associated with a need for improving reverse cholesterol transport comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 41. A method for treatment and/or prophylaxis of conditions associated with a need for decreasing intestinal cholesterol absorption comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 42. A method for treatment and/or prophylaxis of conditions associated with a need for increasing HDL-cholesterol levels comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 43. A method for treatment and/or prophylaxis of conditions associated with a need for decreasing LDL-cholesterol levels comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 44. A method for treatment and/or prophylaxis of inflammatory conditions comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 45. A method for treatment and/or prophylaxis of Alzheimer´s disease comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 46. A method for treatment and/or prophylaxis of arteriosclerosis comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 47. A method for treatment and/or prophylaxis of type 2 diabetes comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

Further aspect 48. A method for treatment and/or prophylaxis of conditions associated with a need for improving HDL function comprising administering to a mammal, including man, in need of such a treatment an effective amount of a compound as defined in any of further aspects 1-18.

For the further aspects 1-48 above the definitions mentioned hereinbefore or the following definitions shall apply:

The term "X" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein said alkyl group may optionally be interrupted by O, S, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2.

The term "Y" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 3 carbon atoms wherein said alkyl group binds to nitrogen in 2-position in the isothiazol-3(2*H*)-one 1,1-dioxide and may optionally be interrupted or ended by O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c and/or Y is optionally substituted by one or more of the following: OH, F, CN, NR^aR^a, C_1-C_4alkyl, OR^b, SR^b, $S(O)R^b$ or SO_2R^b. In the definition of "Y" the term "ended by O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c" means that the alkyl group has as the last position O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$ or NR^c before it binds further to phenyl, heteroaryl, cycloalkyl or heterocyclyl.

The term "Z" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein said alkyl group binds to E or Het^4 and one of the following: Q, Het^1, R or Het^2, and may optionally be interrupted or ended by O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, optionally consists only of one of the following: O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a , SO_2NR^a, NR^aSO_2 and/or Z is optionally substituted by one or more of the following: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $S(O)R^c$, SO_2R^c, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is

optionally substituted by one or more of the following: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b, OR^b. In the definition of "Z" the term "ended by O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2" means that the alkyl group has as the last position O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a or NR^aSO_2 before it binds further to E, Het^4, Q, Het^1, R or Het^2.

The term "M" denotes a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring composed of 4, 5, 6, 7, 8, 9 or 10 carbon atoms.

The term "E" denotes a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring composed of 4, 5, 6, 7, 8, 9 or 10 carbon atoms. The ring binds, unless otherwise specified, through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide.

The term "A" denotes an aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or an aromatic bicyclic ring composed of 4, 5, 6, 7, 8, 9 or 10 carbon atoms.

The term "P" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein the alkyl group binds to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide and is optionally interrupted or ended by O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 and/or P is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $S(O)R^b$, SO_2R^b, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b or OR^b. In the definition of "P" the term "ended by O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2" means that the alkyl group has as the last position O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2" before it binds further to M, Het^3, A or Het^5.

The term "Q" denotes a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7, 8 carbon atoms, which is optionally substituted by one or more of the following:

F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$. Examples of such Q include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl and cyclooctadienyl.

The term "R" denotes a phenyl group which is optionally substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$.

The term "T" denotes an alkyl group having 1 carbon atom or optionally consists of one or more of the following: O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2. T binds to M, Het^3, A or Het^5.

The term "C_1alkyl" denotes an alkyl group having 1 carbon atom. An example of said alkyl includes, but is not limited to, methyl.

The term "C_1-C_3alkyl" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 3 carbon atoms.

The term "C_1-C_4alkyl" denotes a straight or branched, saturated or unsaturated alkyl group having 1 to 4 carbon atoms.

The term "cycloalkyl" denotes a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7, 8 carbon atoms, and includes but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, cyclobutenyl, cyclopentenyl,

cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl and cyclooctadienyl.

The term "heterocyclyl" denotes a saturated or unsaturated non-aromatic 3-8 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon, for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO).

The term "heteroaryl" denotes an aromatic 3-8 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon, for example nitrogen, oxygen and sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO).

The term "Het^1" denotes a saturated or unsaturated non-aromatic 3-10 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon, for example nitrogen, oxygen or sulfur, and wherein the ring optionally is substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO).

The term "Het^2" denotes an aromatic 3-10 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon, for example nitrogen, oxygen and sulfur, and which is substituted by one or more of the following: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or

$NR^aC(O)NR^aR^a$. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO).

The term "Het^3" denotes a saturated or unsaturated non-aromatic 3-10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 4-10 membered bicyclic ring in which one or more of the atoms in the monocyclic or bicyclic ring is an element other than carbon, for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO).

The term "Het^4" denotes a saturated or unsaturated non-aromatic 3-10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 4-10 membered bicyclic ring in which one or more of the atoms in the monocyclic or bicyclic ring is an element other than carbon, for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO). The ring binds, unless otherwise specified, through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide.

The term "Het^5" denotes an aromatic 3-10 membered monocyclic ring or an aromatic 4-10 membered bicyclic ring in which one or more of the atoms in the monocyclic or bicyclic ring is an element other than carbon, for example nitrogen, oxygen or sulfur. The term "sulfur" shall be understood to include sulphoxide (S(O)) and sulphone (SO_2). The term "nitrogen" shall be understood to include nitrogen oxide (NO).

R^a independently represents H or a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F.

R^b independently represents a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F.

R^c independently represents H or a straight or branched, saturated or unsaturated C_1-C_3alkyl chain optionally substituted by one or more F.

The invention is illustrated, but not limited, by the following Examples.

The naming of the compounds in this patent application was made either using a program from ACD Labs (version 6.0/Name, 6.0 Name Batch or labs 8.0/Name) or using the function Autonom 2000 Name in the program Isis Draw.

Examples

Abbreviations

AcOH	acetic acid
Atm	atmosphere
DBU	2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine
DCM	dichloromethane
DIPEA	*N*, *N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*, *N* -dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1*H*-1,2,3-benzotriazole-1-ol
HPFC	high performance flash chromatography
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectroscopy
MeCN	acetonitrile
*M*CPBA	metachloroperbenzoic acid
MeOH	methanol
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
TEA	triethylamine
TFA	trifluoroacetic acid

THF	tetrahydrofuran
UV	ultra violet
rt	room temperature
h	hour(s)
mins	minutes
b	broad
bs	broad singlet
d	doublet
dd	double doublet
m	multiplet
qt	quintet
s	singlet
t	triplet
hep	heptett
ds	double singlett
sep	septett

General Example Experimental Procedures

Phase Separator from IST was used. ISOLUTE SCX-2 were used as cation exchange columns. Flash column chromatography employed normal phase silica gel 60 (0.040-0.063 mm, Merck) or IST Isolute®SPE columns normal phase silica gel or Biotage Horizon HPFC System or a Horizon TM flash system using silica FLASH+ HPFC Cartridges. HPLC purifications were performed on either a Gilson preparative HPLC system with a UV triggered fraction collector, equipped with an ACE C8 5 µm 250 mm x 20 mm column, or a Kromasil C18 column, or on a Waters preparative HPLC system equipped with a Kromasil C8 10 µm 250 mm x 21.2 mm column, or on a Waters preparative HPLC system equipped with an ACE C8 5 µm 250 mm x 50 mm column or an ACE C8 5 µm 250 mm x 20 mm column, or on a Waters FractionLynx HPLC system with a mass triggered fraction collector, equipped with a ACE C8 5µm 100 mm x 21.2 mm column; using MeCN/NH_4OAc buffer system with a gradient from 100% mobilphase A (5% MeCN + 95% 0.1 M NH_4OAc) to 100% mobilphase B (100% MeCN) unless otherwise stated. ^1H NMR and ^{13}C NMR measurements were performed on a BRUKER ACP 300 or on a Varian Unity Plus 400, 500

or 600 spectrometer, operating at ^{1}H frequencies of 300, 400, 500, 600 MHz, respectively, and ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Chemical shifts are given in δ values (ppm) with the solvents used as internal standard, unless otherwise stated. Microwave heating was performed using single node heating in a Smith Creator or Emrys Optimizer from Personal Chemistry, Uppsala, Sweden. Mass spectral data were obtained using a Micromass LCT or Waters Q-Tof micro system and, where appropriate, either positive ion data or negative ion data were collected.

Pyridine N-oxides were prepared by oxidizing the corresponding pyridine compounds with an oxidizing agent such as metachloroperbenzoic acid (MCPBA) in an inert organic solvent such as DCM at rt for 2-24 h.

Synthesis

Starting Material and Intermediates

N-(*tert*-Butyl)-1-phenylmethanesulfonamide

The title compound was prepared as described in the reference below:
Org. Biomol. Chem., 2003, 19, 3390-3395

2-*tert*-Butyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

Potassium *tert*-butoxide (0.845g, 10.56mmol) was added to a solution of N-(*tert*-butyl)-1-phenylmethanesulfonamide (1.2g, 5.28mmol) and diethyl oxalate (0.85mL, 6.33mmol) in THF (8mL) and the mixture was heated at 150°C for 15 mins in a microwave reactor. The reaction mixture was acidified with 1M HCl, the THF was evaporated and the residue was Exampletracted with DCM. Evaporation and trituration of the residue with petroleum ether gave the title compound (7g, 63%) as a solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.32 (m, 5H), 3.90 (br s, 1H), 1.36 (s, 9H); Mass Spectrum: $M\text{-}H^{+}$ 280

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

Oxalyl chloride (3.39g, 2.71mmol) was added dropwise to a solution of 2-*tert*-butyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (5g, 17.77mol) and DMF (15mL) in DCM (220mL) at 0°C. The reaction mixture was heated at 50°C for 4 h, concentrated and the residue was diluted with EtOAc and washed with water, then brine and evaporated. The

residue was purified by silica gel column chromatography, using a 98:2 mixture of petroleum ether and EtOAc as eluant. The product containing fractions were evaporated, the residue was triturated in petroleum ether and the solvent was decanted to give the title compound (3.9g, 74%) as a solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.92 (m, 2H), 7.61-7.51 (m, 3H), 1.75 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 142.8, 132.3, 129.3, 128.8, 123.4, 63.0, 27.7.

4-[(3-Bromopropyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

A solution of TEA (0.18mL, 1.33mmol) in MeCN (5mL) was added dropwise to a mixture of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.20g, 0.67mmol) and (3-bromopropyl)amine hydrobromide (0.146g, 0.67mmol) in MeCN (3mL). After 45 mins a solution of (3-bromopropyl)amine hydrobromide (0.073g, 0.33mmol) and TEA (0.093mL, 0.66mmol) in MeCN (5mL) was added dropwise to the reaction mixture. After 3 h, (3-bromopropyl)amine hydrobromide (0.073g, 0.33mmol) and TEA (0.093mL, 0.66mmol) was added to the reaction mixture. After 17 h the solvent was evaporated and the residue was purified by silica gel column chromatography using 10-20% EtOAc in petroleum ether mixture as eluant, to yield the title compound (0.112g, 42%) as a solid; ^{1}H NMR (500 MHz, CDCl3): δ 7.69-7.50 (m, 2H), 7.50-7.44 (m, 3H), 5.32 (t, 1H), 3.18 (t, 3H), 3.10-3.04 (m, 2H), 1.90-1.78 (m, 2H), 1.76 (s, 9H); Mass Spectrum $M+H^+$ 403.

***N*-Butyl-1-phenylmethanesulfonamide**

The title compound can be prepared as described in the reference below:
Heterocycles, 1993, 36(4), 733-742

2-Butyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N-Butyl-1-phenylmethanesulfonamide (2.0g, 8.80mmol) was dissolved in dry DMF (13mL) under an atmosphere of nitrogen. Diethyl oxalate (1.44g, 9.83mmol) was added and the reaction mixture was cooled to 0°C using an ice-bath. Potassium *tert*-butoxide (1.25g, 11.14mmol) was added in one portion and the reaction mixture was stirred for 5 mins at 0°C, followed by 19 h at rt. The mixture was cooled in an ice-bath and HCl (2M) was carefully added to give a pH~1 of the mixture. Most of the solvents were evaporated and the residue was partitioned between HCl (2M) and EtOAc. The combined organic layers were washed with water several times, dried with $MgSO_4$ and evaporated to dryness. The residue was purified using preparative HPLC (ACE C8, 0.1M NH4OAc/MeCN, gradient) to give the title

compound (0.96 g, 39%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88-7.83 (m, 2H), 7.22-7.29 (m, 3H), 7.14 (bs, 1H), 6.98-7.15 (m, 2H), 3.48 (t, 2H), 1.59-1.67 (m, 2H), 1.27-1.37 (m, 2H), 0.88 (t, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 158.4, 132.3, 128.7, 124.2, 123.2, 37.8, 30.9, 20.2, 14.1; Mass Spectrum: M-H$^+$ 280.

2-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-Butyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (444mg, 1.58mmol) was dissolved in dry DCM (15mL) at rt and under an atmosphere of nitrogen. Oxalyl chloride (0.15mL, 1.73mmol) was added dropwise and the reaction mixture was refluxed for 1.5 h. DMF (0.08mL) was added followed by the addition of oxalyl chloride (0.15mL, 1.73mmol) in 2 portions and the reaction mixture was refluxed for another 6 h. The solvents were evaporated and the residue was partitioned between water and DCM. The combined organic layers were washed with water and the two phases were separated using a phase separator. Evaporation of the organic phase gave the title compound (440mg, 88%) as a brown oil with approximately 95% purity according to ^{1}H-NMR and was used without further purification; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96-8.00 (m, 2H), 7.53-7.62 (m, 3H), 3.74-3.80 (t, 2H), 1.78-1.87 (m, 2H), 1.39-1-50 (m, 2H), 0.98 (t, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.3, 137.1, 132.7, 129.6, 129.2, 127.6, 123.7, 40.9, 30.1, 20.1, 13.7.

N-Isopropyl-1-phenylmethanesulfonamide

The title compound can be prepared as described in the reference below:

Orazi, Orfeo O.; Corral, Renee A.; Bravo, Rodolfo; J.Heterocycl.Chem.; 23; 1986; 1701-1708.

4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

Step A. **Methyl[(benzylsulfonyl)(isopropyl)amino](oxo)acetate**

A mixture of N-isopropyl-1-phenylmethanesulfonamide (1.0g, 4.7mmol) and methyl oxalyl chloride (2.0 mL, 21,6 mmol) was heated at 120°C for 1h. Evaporation gave methyl[(benzylsulfonyl)(isopropyl)amino](oxo)acetate which was used directly in the next reaction without any purification.

Step B. **4-Hydroxy-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide**

Potassium *tert*-butoxide (1.5g, 13.4mmol) was added to a solution of crude methyl[(benzylsulfonyl)(isopropyl)amino](oxo)acetate (2.0g, 21.6mmol) in DMF (15mL).

After 17 h the mixture was evaporated and the residue was purified by silica gel column chromatography using a 4:1 mixture of EtOAc and MeOH as eluant, to give the title compound (0.5g, 40%) as a solid.

Step C **4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide**

DMF (25mL) and oxalyl chloride (0.2mL, 2.29mmol) were added separately to a solution of 4-hydroxy-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.5g, 1.87mmol) in DCM (25mL) at 0 °C. The reaction mixture was then heated at 50°C for 4h, water was added and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with water, then brine and evaporated. The residue was purified by silica gel column chromatography using a 4:1 mixture of hexane and EtOAc as eluant to give the title compound (0.25g, 46 %) as a solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10-7.94 (m, 2H), 7.61-7.50 (m, 3H), 4.50 (sep, 1H), 1.61 (s, 3H), 1.65 (s, 6H).

2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate

The title compound was prepared as described for 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate from 2-*tert*-butyl-4-[(2-hydroxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (Example 76) and 4-methylbenzenesulfonyl chloride with a reaction time of 17h. The reaction mixture was purified by silica gel column chromatography (Horizons Biotage) using 50-100% DCM in petroleum ether 40-60°C as eluent to give the title compound (1.93g, 76%) as a solid; 1H NMR (500MHz, $CDCl_3$): δ 7.76 (d, 1H), 7.46-7.35 (m, 7H), 5.44 (t, 1H), 3.85 (t, 2H), 3.18-3.12 (m, 2H), 2.49 (s, 3H), 1.74 (s, 9H); Mass Spectrum M+H$^+$ 479.

2-*tert*-Butyl-4-[(3-chloropropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

A mixture of 2-*tert*-butyl-4-[(3-hydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (Example 49) (0.14g, 0.42mmol 4-methylbenzenesulfonyl chloride (0.089mg, 0.46mmol) and TEA (0.065ml, 0.46mmol) in DCM (2ml) was stirred at rt for 2h, after which more TEA (0.065ml, 0.46mmol) and cat. DMAP were added. After a further 18h more 4-methylbenzenesulfonyl chloride (0.16mg, 0.84mmol), TEA (0.059ml, 0.42mmol) and DMAP (0.052g, 0.42mmol) were added. After 5h the reaction mixture was warmed to reflux for 18h and evaporated to dryness. The residue was purified by silica gel column chromatography (Horizons Biotage) using 10% EtOAc in hexane as eluent to give the title compound (0.097g,

64%). 1H NMR (500MHz, $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.50-7.44 (m, 3H), 5.32 (t, 1H), 3.35 (t, 2H), 3.08 (q, 2H), 1.80-1.72 (m, 11H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.8, 135.0, 131.8, 130.0, 128.9, 124.9, 107.8, 61.8, 41.7, 41.3, 32.0, 27.8; Mass Spectrum: $M+H^+$ 357.

3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate

A mixture of 2-*tert*-butyl-4-[(3-hydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (Example 49) (2.75g, 8.12mmol), 4-methylbenzenesulfonyl chloride (1.86g, 9.74mmol), DMAP (0.99g, 8.12mmol) and Na_2CO_3 (2.58g, 24.35mmol) in DCM (50ml) was stirred at rt. After 2h the mixture was filtered, evaporated and the residue purified by silica gel column chromatography (Horizons Biotage) using 5:1 DCM/petroleum ether 40-60°C as eluent to give the title compound (2.34g, 58%) as a solid; 1H NMR (500MHz, $CDCl_3$): δ 7.74 (d, 2H), 7.50-7.39 (m, 3H), 7.36 (d, 2H), 5.30 (t, 1H), 3.85 (t, 2H), 2.98 (q, 2H), 2.48 (s, 3H), 1.73 (s, 9H), 1.62 (qt, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.8, 145.4, 134.9, 132.9, 131.8, 130.2, 130.1, 129.0, 128.1, 124.9, 107.9, 67.2, 61.6, 40.3, 28.8, 27.8, 21.9; Mass Spectrum M+H+ 493.

4-[(2-Hydroxyethyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (1.10g, 3.85mmol) was dissolved in dry DMF (10mL) under nitrogen atmosphere. 2-Aminoethanol (0.28g, 4.62mmol) was added followed by TEA (0.58g, 5.77mmol). The reaction mixture was heated in a microwave reactor at 120°C for 15mins. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The residue was purified on a Biotage Horizon HPFC system using Heptane and EtOAc as eluant and TEA as additativ affording the title compound (1.18g, 99.1%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, 6H), 3.02 (q, 2H), 3.57 (t, 2H), 4.38-4.46 (m, 1H), 5.71 (bs, 1H), 7.43-7.46 (m, 3H), 7.50-7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.38, 46.11, 47.76, 60.78, 107.46, 125.22, 128.96, 129.89, 131.70, 135.84, 158.67; Mass Spectrum: $M+H^+$ 311.

2-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate

A mixture of 4-[(2-hydroxyethyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (1.10g, 3.54mmol), 4-toluenesulfonyl chloride (0.81g, 4.25mmol), DMAP (0.43g,

3.54mmol) and Na_2CO_3 (1.13g, 10.63mmol) in dry DCM (20mL) was stirred at rt for 4h. The mixture was filtered and concentrated. The crude product was purified on a Horizon TM flash system using Heptane and EtOAc as eluant and TEA as additative affording the title compound (1.17g, 71.1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, 6H), 2.48 (s, 3H), 3.18 (q, 2H), 3.85 (t, 2H), 4.37-4.45 (m, 1H), 5.47 (t, 1H), 7.37 (d, 2H), 7.40-7.46 (m, 5H), 7.76 (d, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.37, 21.95, 42.80, 47.91, 67.46, 108.77, 124.61, 128.17, 129.19, 130.27, 130.32, 131.54, 132.48, 135.00, 145.74, 158.21; Mass Spectrum: $M+H^+$ 465.

4-[(2-Aminoethyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

Ethylenediamine (0.60g, 10.0mmol) was dissolved in dry DMF (50 ml) and heated to 60°C. 2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (1.00g, 3.34mmol) dissolved in DMF (10 ml) was added droppwise over 30 mins and stirred at 60°C for 10 mins. The reaction mixture was diluted with EtOAc (300 ml) and washed with water (400 ml and 2x200ml), dried (Na_2SO_4), filtered and evaporated to give the title compound (0.97g, 90%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H), 7.42-7.37 (m, 3H), 5.83-5.76 (m, 1H), 2.84-2.78 (m, 2H), 2.67-2.62 (m, 2H), 1.71 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.7, 135.4, 131.6, 129.5, 128.6, 125.2, 106.9, 61.5, 46.2, 40.8, 27.7; Mass Spectrum: $M+H^+$ 324.

4-[(4-Hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.15g, 0.53 mmol), 4-aminocyclohexanol (0.092g, 0.80 mmol) and TEA (0.081g, 0.80 mmol) was dissolved in dry MeCN (3 ml). The reaction was heated in a microwave reactor at 120°C for 10 mins. A few extra drops of 4-aminocyclohexanol was added and the reaction was heated in a microwave reactor at 140°C for 20 mins. The residue was purified by silica gel column chromatography using a 25:75 mixture of hexane and EtOAc, to give a 50:50 mixture of cis and trans isomers (0.130g, 67%). The mixture was separated by HPLC (C8, 0.05M NH4OAc (pH=4.1):MeCN 1:1) to give cis (Example 38) and trans (Example 48) isomers.

***N*-(2-Methoxyethyl)-1-phenylmethanesulfonamide**

Phenylmethanesulfonyl chloride (3.0g, 15.7mmol) was dissolved in dry THF (15mL) and it was added dropwise to a solution of 2-methoxyethylamine (2.36g, 31.5mmol) in dry THF (50mL) at 0°C. After addition the ice-bath was removed and the reaction was stirred at rt for

2.5 h. The solvent was removed in vacuo and the residue was dissolved in DCM. The mixture was washed with one portion of 5% aqueous HCl, several portions of water, dried through a phase separator and evaporated to give the title compound (3.58g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.35 (m, 5H), 4.52 (br s, 1H), 4.26 (s, 2H), 3.40 (t, 2H), 3.32 (s, 3H), 3.14-3.09 (m, 2H); Mass Spectrum: M-H$^+$ 228.

4-Hydroxy-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

A solution of *N*-(2-methoxyethyl)-1-phenylmethanesulfonamide (3.5 g, 14.5 mmol) and diethyl oxalate (2.33g, 16.0mmol) in dry DMF was cooled in an ice-bath. Potassium tert-butoxide (2.17g, 18.4mmol) was added and after 5 mins the ice-bath was removed and the reaction was stirred at rt for 22 h. 2M HCl (45mL) was added to the mixture and the acidic solution was extracted 3 times with dichloromethane. The combined organic layers were washed 4 times with water, dried through a phase separator and evaporated. The residue was purified by preparative HPLC [0.1M NH_4OAc/MeCN, (9:1 to 1:9)] to give the title compound (0.250 g, 6%) as a solid; ^{1}H NMR (500 MHz, CD_3OD): δ 7.90-7.94 (m, 2H), 7.28-7.33 (m, 2H), 7.10-7.15 (m, 1H), 3.79 (t, 2H), 3.68 (t, 2H), 3.34 (s, 3H); Mass Spectrum: M-H$^+$ 282.

4-Chloro-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

Oxalyl chloride (0.185g, 1.46mmol) was added dropwise to a solution of 4-hydroxy-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.250g, 0.88mmol) in DCM (15 mL). The mixture was refluxed for 2 days and then evaporated. The residue was dissolved in water and extracted 3 times with dichloromethane. The combined organic layers were washed 2 times with water, dried through a phase separator and evaporated to give the title compound (0.245g, 92%) as a solid; ^{1}H NMR (500 MHz, CD_3OD): δ 7.94-7.97 (m, 2H), 7.58-7.67 (m, 3H), 3.94 (t, 2H), 3.70 (t, 2H), 3.38 (s, 3H).

N-Ethyl-1-phenylmethanesulfonamide

The title compound was prepared as described in the reference below:

Orazi, Orfeo O.; Corral, Renee A.; Bravo, Rodolfo; J. Heterocycl. Chem.; 23; 1986; 1701-1708.

2-Ethyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N-Ethyl-1-phenylmethanesulfonamide (20g) was divided into batches of 0.5g each and taken in an 8mL vial. To each vial was added potassium tert-butoxide (0.426g, 3.8mmol), ethyl oxalate (0.408mL, 3.01mmol) and dry THF (4mL). Each vial was heated in a microwave reactor at 145°C for 20 mins. Reaction mixture from all the vials were combined and treated with 1.5 N HCl (75mL) and extracted with EtOAc. The organic layers were washed with water (3 x 25mL) and brine, dried over Na_2SO_4 and evaporated. A small amount of the DCM was added to the solid residue and stirred well. Filtration gave nearly pure title compound (21g, 82.6%) as off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, 3H, J = 7.2 Hz), 3.8 (q, 2H, J = 7.2 Hz), 7.3-7.5 (m, 3H), 7.9 – 8.0 (m, 2H).

4-Chloro-2-ethyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-Ethyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (5g, 19.76mmol) was dissolved in dry DCM (250mL) and cooled to 0°C under N_2. Dry DMF (15mL) was added, followed by oxalyl chloride (3mL, 34.4mmol). The ice-bath was removed and the mixture was refluxed at 50°C under N_2 for 4 h. The reaction mixture was evaporated and the residue was diluted with EtOAc, washed with water (3 x 25mL) and brine, dried over Na_2SO_4 and evaporated. Another (16g, 63.24mmol) of 2-ethyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide was dissolved in dry DCM (500mL) and cooled to 0°C under N_2. Dry DMF (20mL) was added followed by oxalyl chloride (9 mL, 103.2 mmol). The ice-bath was removed and the mixture was refluxed at 50°C under N_2 for 4 h. The reaction mixture was evaporated and the residue was diluted with EtOAc, washed with water (3 x 50mL) and brine, dried over Na_2SO_4 and evaporated where by red solid was obtained. The crude material from both batches were combined and purified by column chromatography on silica gel using 2.5-3 % ethyl acetate in petroleum ether as eluant, and recrystallised from methanol to give the title compound (15.7g, 70%) as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (t, 3H, J = 7.3 Hz), 3.84 (q, 2H, J = 7.3 Hz), 7.6 – 7.7 (m, 3H), 7.9 – 8.0 (m, 2H); Mass Spectrum: $M+H^+$ 272.

Methyl 4-{3-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoate

The title compound was prepared as described for Example 5 from 2-*tert*-butyl-4-[(3-bromopropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and methyl 3-hydroxybenzoate at a temperature of 100°C. The residue was purified by flash chromatography using hexane and EtOAc as eluent to give the title compound (0.124g, 49%).

4-{2-[1,1-Dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

A mixture of 4-{2-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate (Example 77) (0.160g, 0.334mmol) in TFA (1ml) was heated in a microwave reactor at 120°C for 25mins. The reaction mixture was evaporated to dryness and the residue purified by silica gel column chromatography (Horizons Biotage) using 6-12% MeOH in EtOAc (+1% AcOH) as eluent to give the title compound (0.047g, 43%) as a solid; ^{1}H NMR (500MHz CD_3OD): δ 7.54-7.47 (m, 5H), 7.13 (d, 2H), 6.84 (d, 2H), 3.20-3.14 (m, 5H), 2.56 (t, 2H); ^{13}C NMR (125MHz CD_3OD): δ 164.2, 148.4, 137.9, 136.7, 131.5, 130.1, 129.1, 128.5, 127.1, 121.9, 108.2, 44.4, 36.2, 34.9; Mass Spectrum: $M+H^+$ 423

Methyl [(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetate

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (1.09g, 3.64mmol), methyl glycinate hydrochloride (0.68g, 5.46mmol) and TEA (1.10g, 10.92mmol) were dissolved in a mixture of MeCN (10mL) and DMF (5mL) and the reaction mixture was stirred at 65°C over night. The reaction mixture was evaporated and the residue was diluted with saturated aqueous $NaHCO_3$ and the mixture was extracted with DCM. The organic phases were combined, dried over $MgSO_4$, filtered and evaporated to give the title compound.

[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetic acid

Methyl [(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetate (1.28g, 3.64mmol) was dispersed in a mixture of dioxane (20mL), MeOH (20mL) and water (20mL). Aqueous LiOH (1M, 0.218g, 9.10 mmol) was added and the reaction mixture was stirred at rt for 2 h. Aqueous HCl was carefully added to the reaction mixture to give the pH~1 and the resulting mixture was extracted with DCM. The organic phases were combined, dried over Na2SO4, filtered, evaporated and the crude residue was purified by preparative HPLC giving the title comound (0.51g, 41%). ^{1}H-NMR (CD_3OD, 500 MHz): δ 7.52-7.48 (m, 2H), 7.46-7.42 (m, 3H), 5.41 (brs, 8H) 1.95 (s, 2H), 1.71 (s, 9H); ^{13}C-NMR (CD_3OD, 125 MHz): δ 178.4, 174.8, 160.8, 136.5, 132.8, 130.4, 129.5, 126.6, 107.4, 62.1, 48.3, 27.9, 22.9.

***tert*-Butyl [1-(2-cyanoethyl)piperidin-4-yl]carbamate**

3-Bromopropionitril (0.74g, 5.49mmol) was added to a solution of *tert*-butyl piperidin-4-ylcarbamate (1.00g, 4.99mmol) and TEA (0.56 g,5.49mmol) in MeCN (15mL), and the mixture was heated at 60°C for 5h and then evaporated. The residue was purified by silica gel column chromatography (Horizons Biotage) using a 40:60 and then 15:85-10:90 mixture of heptane and EtOAc as eluant, to give the title compound (0.40g, 32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.44 (br s, 1H), 3.54-3.42 (br m, 1H), 2.88-2.79 (m 2H), 2.69 (t, 2H), 2.51 (t 2H), 2.24-2.16 (m, 2H), 1.99-1.92 (m 2H), 1.47 (s 9H), 1.49-1.41 (m 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 119.0, 53.6, 52.2, 47.7, 32.7, 28.6, 16.4.

3-(4-Aminopiperidin-1-yl)propanenitrile

TFA (1.21g, 10.62mmol) was added to a solution of *tert*-butyl [1-(2-cyanoethyl)piperidin-4-yl]carbamate (0.27g, 1.06mmol) in DCM (11mL), and the mixture was stirred at rt for 2 h. The mixture was evaporated and the product was used without any futher purification.

2-(4-Phenoxybutyl)-1*H*-isoindole-1,3(2*H*)-dione

A mixture of N-(4-bromobutyl)phthalimide) (2.00g, 7.09mmol), phenol (0.67g, 7.09) and K_2CO_3 (1.96g, 14.18mmoml) in dry MeCN (30ml) was stirred at rt for 66h. The reaction mixture was then warmed to 50°C for 20h before more phenol (0.33mg, 3.54mmol) was added and the resulting mixture was warmed at reflux. After 4h EtOAc was added, the mixture was washed with brine, then 1N NaOH, and brine again before evaporated the organic phase to dryness to give the title compound (1.11g, 53%) which was used without further purification. ^{1}H NMR (500MHz $CDCl_3$): δ 7-90-7.83 (m, 2H), 7.76-7.70 (m, 2H), 7.28 (t, 2H), 6.93 (t, 1H), 6.89 (d, 2H), 4.01 (t, 2H), 3.79 (t, 2H), 1.96-1.82 (m, 4H); Mass Spectrum: M+H$^+$ 296.

(4-Phenoxybutyl)amine

A mixture of 2-(4-phenoxybutyl)1*H*-isoindole-1,3(2*H*)-dione (1.10g, 3.27mmol) and 25% hydrazine solution in water (2.88ml, 13.10mmol) in EtOH (30ml) was warmed at reflux. After 1.5h, EtOAc was added and the mixture was extracted with brine. The combined aqueous phases were then re-extracted with EtOAc and all the organic phases combined. These were then extracted with 1N HCl, the acidic aqueous phases combined, basified with 2N NaOH and re-extracted into EtOAc before evaporating to dryness to give the title

compound (0.411mg, 67%) as an oil. ^{1}H NMR (500MHz $CDCl_3$): δ 7.32-2.26 (m, 2H), 6.95 (t, 1H), 4.00 (t, 2H), 2.80 (t, 2H), 1.90-1.82 (m, 2H), 1.68-1.62 (m, 2H).

tert-Butyl [2-(4-hydroxyphenyl)ethyl]carbamate

4-(2-Aminoethyl)phenol (2.00g, 14.58mmol) was dissolved in THF (70mL) and MeOH (10mL) and TEA (1.47g, 14.58mmol) was added. The mixture was cooled in an ice-bath. Di-_tert_-butyl dicarbonate (3.18g, 14.58mmol) was added. The mixture was stirred for 1h at 0°C and left at rt overnight. The solvent was evaporated and column chromatography of the crude product (ISOLUTE SI, (20g), eluated with Heptane/EtOAc (90:10), Heptane/EtOAc (70:30)) afforded the title compound (3.47g, 100%). ^{1}H NMR (500MHz, CD_3OD): δ 1.43 (s, 9H), 2.66 (t, 2H), 3.20 (t, 2H), 6.72 (d, 2H), 7.02 (d, 2H); Mass Spectrum: M-H$^+$ 236.

4-{2-[(_tert_-Butoxycarbonyl)amino]ethyl}phenyl methanesulfonate

tert-Butyl [2-(4-hydroxyphenyl)ethyl]carbamate (3.45g, 14.54mmol) was dissolved in dry DCM (70mL) and cooled in an ice-water bath. Methanesulfonyl chloride (1.99g, 17.45mmol) was added followed by TEA (2.21g, 21.80mmol). The reaction mixture was stirred at rt for 2h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, and the organic phase was dried with $MgSO_4$, filtered and evaporated. Column chromatography of the crude product (ISOLUTE SI, (20g), eluated with Heptane/EtOAc (90:10), Heptane/EtOAc (70:30)) afforded the title compund (4.06g, 88.5%). ^{1}H NMR (500MHz, CD_3OD): δ 1.43 (s, 9H), 2.80 (t, 2H), 3.20 (s, 3H), 3.29 (q, 2H), 7.25 (d, 2H), 7.31 (d, 2H).

4-(2-Aminoethyl)phenyl methanesulfonate

4-{2-[(_tert_-Butoxycarbonyl)amino]ethyl}phenyl methanesulfonate (3.98g, 12.62mmol) was dissolved in DCM (12mL) and TFA (10mL) and stirred at rt for 4h. The reaction mixture was concentrated and redissolved in EtOAc, washed with saturated aqueous K_2CO_3, and the organic phase was dried with Na_2SO_4, filtered and evaporated affording the title compound (2.71g, 99.8%). ^{1}H NMR (500MHz, CD_3OD): δ 2.79 (t, 2H), 2.89 (t, 2H), 3.21 (s, 3H), 7.26 (d, 2H), 7.32 (d, 2H); ^{13}C NMR (125MHz, CD_3OD): δ 36.24, 38.34, 42.95, 122.11, 130.19, 139.44, 148.28; Mass Spectrum: M+H$^+$ 216.

tert-Butyl 3-(2-amino-2-oxoethyl)azetidine-1-carboxylate

PyBOP (1.946g, 3.74mmol) was added to a solution of [1-(*tert*-Butoxycarbonyl)azetidin-3-yl]acetic acid (0.805g, 3.74 mmol) in DMF (10mL). The mixture was stirred in an ice-bath, ammonia gas was bubbled in for 3 mins and then the mixture was stirred at rt overnight. The reaction mixture was concentrated, water (15mL) and saturated, aqueous $NaHCO_3$ (5mL) were added, and the mixture was extracted with EtOAc (20mLx3). The extracts were combined, washed with water (20mL) and brine (10mL), dried (Na_2SO_4) and evaporated. Column chromatography of the residue (ISOLUTE SI, 50g/150 ml), eluting with EtOAc and heptane (50:50), then EtOAc and then MeOH and EtOAc (1:99, 2:98 and 5:95), gave the title compound (0.461g, 57.5%) as a white solid. ^{1}H NMR (400 MHz, CDCl3): 1.42 (s, 9H), 2.53 (d, 2H), 2.85-2.96 (m, 1H), 3.60 (dd, 2H), 4.09 (t, 2H), 5.78 (s, br, 2H); ^{13}C NMR (100 MHz, CDCl3): 25.4, 28.3, 39.7, 54.3 (br), 79.4, 156.3, 173.2.

***tert* -Butyl 3-(2-aminoethyl)azetidine-1-carboxylate**

tert-Butyl 3-(2-amino-2-oxoethyl)azetidine-1-carboxylate (70mg, 0.327mmol) was dissolved in THF (2mL) and cooled on an ice-bath. Borane dimethyl sulfide complex (0.41mL, 2M in THF) was added droppwise, whereafter the mixture was refluxed for 6 h. The reaction mixture was allowed to attain rt and a mixture of DIPEA:MeOH (0.6mL, 1:2) and iodine (166mg, 0.654mmol) was added. The mixture was stirred at rt overnight and then evaporated to dryness. Water (5mL) and EtOAc (5mL) were added to the residue an the two phases were separated. Saturated, aqueous $NaHCO_3$ (1mL) was added into the water phase, and it was extracted with EtOAc (5mLx4). NaOH (1M, ca 1mL) was added into the water phase and it was extracted with EtOAc (5mLx2). The extracts were combined, dried (Na_2SO_4) and evaporated, and the residue was purified by using an ion exchange column (ISOLUTE PRS, 2g/15mL), eluting with MeOH and DCM (10:90), then MeOH and then MeOH (saturated with NH_3) to give the title compound (35mg, 53.5%). ^{1}H NMR (400 MHz, CDCl3): 1.41 (s, 9H), 1.71 (dt, 2H), 2.49-2.60 (m, 1H), 2.64 (t, 2H), 3.54 (dd, 2H), 3.99 (t, 2H); ^{13}C NMR (100 MHz, CDCl3): 26.6, 28.3, 38.3, 39.8, 54.3 (br), 79.1, 156.3.

***tert*-Butyl [2-(4-bromophenyl)ethyl]carbamate**

[2-(4-Bromophenyl)ethyl]amine (2.20g, 11.00mmol) was dissolved in dry THF (77mL) and TEA (1.11g, 11.00mmol) was added. The mixture was cooled in an ice-bath. Di-*tert*-butyl dicarbonate (2.40g, 11.00mmol) was added. The mixture was stirred for 1h at 0°C and left at rt overnight. The solvent was evaporated and column chromatography of the crude product

(ISOLUTE SI (20g), Heptane/EtOAc (90:10)) afforded the title compound (3.18g, 96.3%). ^{1}H NMR (500MHz, CD_3OD): δ 1.42 (s, 9H), 2.73 (t, 2H), 3.25 (t, 2H), 7.14 (d, 2H), 7.43 (d, 2H).

tert-Butyl [2-(4-cyanophenyl)ethyl]carbamate

tert-Butyl [2-(4-bromophenyl)ethyl]carbamate (0.52g, 1.73mmol) was dissolved in dry DMF (17mL) under nitrogen atmosphere. Zinc cyanide (0.41g, 3.46mmol) and tetrakis(triphenylphosphine)palladium (0.16g, 0.14mmol) was added. The reaction mixture was heated in a microwave reactor at 150°C for 20mins. The procedure was repeated two more times with equal amount of starting material and the resulting three mixtures were combined. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and water, dried with Na_2SO_4, filtered and evaporated. The crude product was purified using Biotage Horizon HPFC system (40+M column, isocratic run DCM/MeOH (99.5:0.5, 960mL), gradient run DCM/MeOH (99.5:0.5-92:8, 240mL), isocratic run DCM/MeOH (92:8, 720mL)) affording the title compound (1.14g, 88.9%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.88 (t, 2H), 3.40 (q, 2H), 4.58 (bs, 1H), 7.32 (d, 2H), 7.61 (d, 2H); Mass Spectrum: $M+H^+$ 247.

4-(2-Aminoethyl)benzonitrile

tert-Butyl [2-(4-cyanophenyl)ethyl]carbamate (1.14g, 4.62mmol) was dissolved in DCM (6mL) and TFA (5mL) was added. The mixture was concentrated and dissolved in EtOAc, and the organic phase was washed with saturated aqueous K_2CO_3. The organic layer was dried with Na_2SO_4, filtered and evaporated affording the title compound (0.50g, 74.3%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.21 (bs, 2H), 2.81 (t, 2H), 2.99 (t, 2H), 7.31 (d, 2H), 7.58 (d, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 40.38, 43.31, 110.33, 119.23, 129.86, 132.48, 145.93.

tert-Butyl 3-hydroxypyrrolidine-1-carboxylate

tert-Butyl 3-oxopyrrolidine-1-carboxylate (3.00g, 16.20mmol) was dissolved in dry MeOH (60mL) and cooled in an ice-water bath. Sodium borohydride (0.61g, 16.20mmol) was added carefully and the reaction mixture was stirred at 0°C for 15mins. The reaction mixture was diluted with water and pH was set to ~9 with HCl (1% aqueous solution). The aqueous layer was extracted with EtOAc and the organic layers were combined, dried with $MgSO_4$, filtered and evaporated to give the title compound (3.00g, 98.9%). ^{1}H NMR (500MHz, $CDCl_3$): δ

1.42 (s, 9H), 1.85-1.96 (m, 2H), 3.26-3.33 (m, 2H), 3.38-3.47 (m, 3H), 4.38-4.40 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.72, 33.95, 43.99, 54.38, 70.60, 79.57, 155.07.

***tert*-Butyl 3-[(methylsulfonyl)oxy]pyrrolidine-1-carboxylate**

tert-Butyl 3-hydroxypyrrolidine-1-carboxylate (3.00g, 16.02mmol) was dissolved in dry DCM (50mL) and cooled in an ice-water bath. Methanesulfonyl chloride (2.38g, 20.83mmol) was added followed by TEA (2.43g, 24.03mmol) and the reaction mixture was stirred at 0°C for 3.5h. The reaction mixture was washed with water (250mL) and dried with $MgSO_4$, filtered and evaporated. The crude product was purified using Biotage Horizon HPFC system (40+M column, isocratic run heptane/EtOAc (50:50)) affording the title compund (2.70g, 63.5%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.07 (bs, 1H), 2.18 (bs, 1H), 2.97 (s, 3H), 3.35-3.61 (m, 4H), 5.16-5.18 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.59, 31.84, 32.76, 38.80, 43.61, 52.16, 80.12, 154.30.

***tert*-Butyl 3-(acetylthio)pyrrolidine-1-carboxylate**

Potassium carbonate (4.42g, 31.96mmol) was suspended in dry MeOH (20mL) and thioacetic acid (2.28g, 29.96mmol) was added. The mixture was stirred vigorously for 10 mins, concentrated and diluted in dry DMF (30mL). *tert*-Butyl 3-[(methylsulfonyl)oxy]pyrrolidine-1-carboxylate (2.65g, 9.99mmol) dissolved in dry DMF (20mL) was added and the reaction mixture was heated to 60°C for 3.5h. The reaction mixture was diluted with water (350mL) and extracted with EtOAc (2x150mL) The organic phases were dried with $MgSO_4$, filtered and evaporated. The crude product was purified using Biotage Horizon HPFC system (25+M column, isocratic run heptane/EtOAc (60:40)) affording the title compund (0.592g, 24.2%) (the product is a mixture of cis and trans isomers).^{1}H NMR (500MHz, $CDCl_3$): δ 1.41 (d, 18H), 1.66 (d, 1H), 1.74-1.86 (m, 2H), 2.20-2.26 (m, 2H), 2.29 (s, 3H), 3.10-3.26 (m, 2H), 3.30-3.43 (m, 4H), 3.46-3.54 (m, 1H), 3.66-3.74 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.68, 30.82, 31.25, 32.34, 36.16, 41.09, 44.88, 51.60, 55.37, 79.67, 154.43; Mass Spectrum: $M+H^+$ 241.

***tert*-Butyl 3-mercaptopyrrolidine-1-carboxylate**

tert-Butyl 3-(acetylthio)pyrrolidine-1-carboxylate (200mg, 0.81mmol) was dissolved in MeOH (10mL) and sodium methanethiolate (57mg, 0.81mmol) was added. The reaction mixture was stirred at rt for 30mins. HCl (1M solution) was added and the aqueous layer

extracted with DCM. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated affording the title compund (0.163g, 98.4%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.68 (d, 1H), 1.75-1.84 (m, 1H), 2.22-2.28 (m, 1H), 3.13-3.23 (m, 1H), 3.30-3.40 (m, 2H), 3.47-3.57 (m, 1H), 3.67-3.74 (m, 1H).

[3-(Pyridin-2-yloxy)propyl]amine

3-Aminopropan-1-ol (0.28ml, 3.64mmol) was added to a mixture of NaH 60% dispersion in mineral oil (16mg, 4.11mmol) in dry THF (8ml) at rt. The resulting mixture was heated at reflux for 35mins and cooled to rt before 2-bromopyridine (0.50g, 3.16mmol) was added. The mixture was then refluxed for 2h 20mins and stirred at rt for another 17h before more NaH (127mg, 3.16mmol) was added and the mixture heated at reflux for 3h. The mixture was evaporated to dryness, water was added, and the mixture was acidified to pH5 with 1N HCl and washed with DCM. The aqueous phase was then basified to pH4 and extracted again with DCM. The organic extracts were combined and evaporated to give the title compound (0.206g, 43%) as an oil. ^{1}H NMR (500MHz $CDCl_3$): 8.17-8.12 (m, 1H), 7.58-7.53 (m, 1H), 6.67-6.63 (m, 1H), 6.72 (d, 1H), 4.39 (t, 2H), 2.88 (t, 2H), 1.93 (quintet, 2H). ^{13}C NMR (125MHz CDCl3): 164.1, 147.1, 138.7, 116.8, 111.3, 63.8, 39.5, 33.3.

***tert*-Butyl [1-(5-methylpyridin-2-yl)piperidin-4-yl)carbamate**

A solution of 2-bromo-5-methylpyridine (1.00g, 5.8mmol), tert-butyl piperidine-4-ylcarbamate (1.28g, 6.39mmol) and TEA (1.21ml, 8.72mmol) in DMSO (5ml) was heated at 110°C, After 17h the reaction mixture was heated at 130°C for 4h before more TEA (0.40ml, 2.91mmol) was added. After 2.5h, DBU (1.73ml, 11.63mmol) was added and the reaction mixture heated at 110°C for 17h. The reaction mixture was then allowed to cool to rt and EtOAc was added. The reaction mixture was washed with brine and evaporated to dryness. The residue was purified using the Biotage SP1 eluting with 25% EtOAc in pet. ether 40-60°C to give the title compound (0.233g, 14%) as a solid. ^{1}H NMR(500MHz, $CDCl_3$): 8.02 (d, 1H), 7.31 (dd, 1H), 6.62 (d, 1H), 4.48 (bs, 1H), 4.16-4.10 (m, 2H), 3.68 (bs, 1H), 2.95 (dt, 2H), 2.20 (s, 3H), 2.08-2.00 (m, 2H), 1.48-1.40 (m, 9H). ^{13}C NMR($CDCl_3$): 158.1, 155.4, 147.9, 138.6, 122.3, 107.5, 79.5, 48.4, 45.1, 32.3, 28.7, 17.5. Mass Spectrum: M+H 292.

1-(5-Methylpyridin-2-yl)piperidin-4-amine dihydrochloride

A solution of tert-butyl [1-(5-methylpyridin-2-yl)piperidin-4-yl)carbamate (0.23g, 0.79mmol) in HCl in Dioxane (4M, 2ml), THF (1ml) and MeOH (1ml) was stirred at room temperature. After 17h, the reaction mixture was filtered, and the residue washed with EtOAc and dried to give the title compound (181mg, 86.8%) as a solid. ^{1}H NMR(500MHz, D_2O): 7.80 (d, 1H), 7.60 (s, 1H), 7.15 (d, 1H), 4.10-4.03 (m, 2), 3.53-3.44 (m, 1H), 3.21 (t, 2H), 2.16-2.10 (m, 5H), 1.65 (dq, 2H); ^{13}C NMR(D_2O): 150.8, 146.8, 133.9, 123.9, 112.9, 47.7, 44.7, 28.8; Mass Spectrum: M+H 192

tert-Butyl [1-(6-chloropyridazin-3-yl)piperidin-4-yl]carbamate

tert-Butyl piperidin-4-ylcarbamate (2g, 10 mmol), 3,6-dichloropyridazine (1.79g, 12 mmol) and TEA (2.1 ml, 15 mmol) was dissolved in dry DMF (30 ml) and the reaction mixture was heated in a microwave reactor at 150°C for 20 mins. The reaction mixture was diluted with water (300 ml) and extracted with EtOAc (300 ml). The organic phase was dried (Na_2SO_4), filtrated and evaporated. The residue was purified by silica gel column chromatography using a 98:2 mixture of DCM:MeOH to give the title compound (2.11g, 68%) as a solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, 1H), 6.91 (d, 1H), 4.48 (bs, 1H), 4.29-4.20 (m, 2H), 3.73 (bs, 1H), 3.14-3.04 (m, 2H), 2.10-2.02 (m, 2H), 1.49-1.38 (m, 2H), 1.45 (s, 9H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 158.9, 155.2, 146.7, 128.9, 115.5, 79.6, 47.9, 44.4, 31.9, 28.5.

1-(6-Chloropyridazin-3-yl)piperidin-4-amine

[1-(6-Chloro-pyridazin-3-yl)-piperidin-4-yl]-carbamic acid tert-butyl ester (0.59g 1.89 mmol) was dissolved in THF:MeOH 2:1 (45 ml) and HCl in 1,4-dioxan (4M, 3.8 ml, 7.56 mmol) was added. The reaction was stirred at rt for 3h and then att 60°C for 2h. The solvent was evaporated to yield the title compound (0.49g, 100%) as the hydrochloric salt. ^{1}H-NMR (CD_3OD, 500 MHz): δ 8.10 (d, 1H), 7.92 (d, 1H), 4.41-4.35 (m, 2H), 3.67-3.57 (m, 1H), 3.55-3.46 (m, 2H), 2.32-2.24 (m, 2H), 1.96-1.83 (m, 2H).

tert-Butyl [1-(6-methoxypyridazin-3-yl)piperidin-4-yl]carbamate

tert-Butyl [1-(6-chloropyridazin-3-yl)piperidin-4-yl]carbamate (0.50g, 1.60 mmol) was dissolved in dry MeOH (15 ml) and sodium metal (0.073g, 3.20 mmol) dissolved in MeOH (5 ml) was added. The reaction mixture was heated at in a microwave reactor at120°C for 4h. The mixture was diluted with water (500 ml) and extracted with EtOAc (200 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated to yield the title compound (0.37g, 75%).

1-(6-Methoxypyridazin-3-yl)piperidin-4-amine

[1-(6-Methoxy-pyridazin-3-yl)-piperidin-4-yl]-carbamic acid tert-butyl ester (0.37, 1.2 mmol) was dissolved in THF:MeOH 9:1 (15 ml) and HCl in 1,4-dioxane (4M, 1.2 ml, 4.8 mmol) was added. The reaction mixture was heated to 60°C with for 3h. The solvent was evaporated to yeld the title compound (0.35g, 100%) as the dihydrochloric salt. ^{1}H-NMR (CD_3OD, 500 MHz): δ 8.04 (d, 1H), 7.57 (d, 1H), 4.34-4.26 (m, 2H), 4.00 (s, 3H), 3.62-3.55 (m, 1H), 3.50-3.40 (m, 2H), 2.30-2.23 (m, 2H), 1.90-1.79 (m, 2H); ^{13}C-NMR (CD_3OD, 125 MHz): δ 159.7, 152.1, 129.8, 127.0, 62.1, 55.9, 46.2, 45,9, 45.7, 30.9, 30.3, 30.1.

***tert*-Butyl (1-pyridazin-3-ylpiperidin-4-yl)carbamate**

tert-Butyl [1-(6-chloropyridazin-3-yl)piperidin-4-yl]carbamate (0.5g, 1.60 mmol) was dissolved in MeOH (20 ml) and cooled to 0°C with an icebath. 10% Pd/C (60 mg) was added carefully. Ammonium formate (0.30g, 4.80 mmol) was added and the reaction mixture was heated to 40°C. Ammonium formate (0.604g, 9.59 mmol) was added in portions during the reaction, after 33h at 40°C the reaction mixture was filtered through celite and the celite was washed with MeOH (20 ml). The reaction mixture was evaporated and the residue was diluted with EtOAc (100mL) and washed with water (200 ml). The organic phase was dried (Na_2SO_4) filtered and evaporated. The residue was purified by silica gel column chromatography using a 98:2 mixture of DCM:MeOH to give the title compound as a solid (0.25g, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.52-8.47 (m, 1H), 7.17-7.11 (m, 1H), 6.91-6.84 (m, 1H), 4.67-4.57 (m, 1H), 4.30-4.21 (m, 2H), 3.75-3.62 (m, 1H), 3.09-2.99 (m, 2H), 2.05-1.96 (m, 2H), 1.46-1.35 (m, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 155.4, 143.3, 127.5, 112.7, 79.6, 48.2, 44.3, 32.1, 28.6.

1-Pyridazin-3-ylpiperidin-4-amine

tert-Butyl (1-pyridazin-3-ylpiperidin-4-yl)carbamate (0.22g, 0.92 mmol) was dissolved in THF:MeOH 70:30 (15 ml) and HCl in 1,4-dioxane (4M, 1.84 ml, 7.36 mmol) was added and the mixture was refluxed for 1.5h. The reaction mixture was evaporated to yield the title compound (0.250g, 100%) as the dihydrochloric salt. (0.250g, 100%). ^{1}H NMR (CD_3OD, 500 MHz): δ 8.72-8.67 (m, 1H), 8.14-8.07 (m, 1H), 8.03-7.97 (m, 1H), 4.55-4.45 (m, 2H), 3.62-3.51 (m, 1H), 3.38-3.27 (m, 2H), 2.27-2.18 (m, 2H), 1.82-1.70 (m, 2H)

***Tert*-Butyl{1-[3-chloro-5-(trifluoromethyl)pyridine-2-yl]piperidin-4-yl}carbamate**

A mixture of 2,3-dichloro-5-(trifluoromethyl)pyridine (2.0g, 9.26mmol), *tert*-butyl piperidine-4-ylcarbamate (2.2g, 11.11mmol) and anhydrous potassium carbamate (3.8g, 27.78mmol) in DMF (15ml) was heated in a microwave reactor at 150°C for 10min. The mixture was concentrated, water and EtOAc were added to the residue and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc 90:10) to yield the title compound (2.5g, 70%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.47 s, 9H), 1.53-1.60 (m, 2H), 2.07-2.09 (m, 2H), 3.01-3.06 (m, 2H), 3.72 (br.s., 1H), 3.97-4.00 (m, 2H), 4.54 (br.s., 1H), 7.75 (s, 1H), 8.38 (s, 1H); Mass Spectrum: M+H$^+$ 380.

1-[3-Chloro-5-(trifluoromethyl)-pyridin-2-yl]piperidine-4-amine

tert-Butyl{1-[3-chloro-5-(trifluoromethyl)pyridine-2-yl]piperidin-4-yl}carbamate (2.5g, 6.4mmol) was stirred in a mixture of THF (25ml), MeOH (5ml) and HCl in dioxane (4M, 6.5ml) over night at rt. HCl in dioxane (4M, 4ml) was added and after 4h a third portion of HCl in dioxane /4M, 4ml) was added. Stirring was continued for 48h at rt. The solvent was evaporated, and the residue was dissolved in EtOAc. The resulting mixture was washed with aqueous saturated Na_2CO_3, water and dried over Na_2SO_4. Concentration of the organic phase yielded the title compound (2.3g, 128%), which contained some impurities. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.50-1.54 (m, 2H), 1.88-1.94 (m, 2H), 2.93-3.00 (m, 3H), 4.01-4.04 (m, 2H), 7.74 (s, 1H), 8.38 (s, 1H); Mass Spectrum: M+H$^+$ 280.

2-(Benzyloxy)phenyl methanesulfonate

2-(Benzyloxy)phenol (3.00g, 14.98mmol) was dissolved in dry DCM (70mL) under nitrogen atmosphere and cooled on an ice-water bath. Methanesulfonyl chloride (2.06g, 17.98mmol) was added during stirring followed by TEA (2.27g, 22.47mmol). The reaction mixture was stirred at rt for 2h and then washed with aqueous saurated $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated affording the title compund (4.04g, 96.9%). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.09 (s, 3H), 5.15 (s, 2H), 7.02 (dt, 1H), 7.09 (dd, 1H), 7.27 (dt, 1H), 7.34-7.48 (m, 6H); ^{13}C NMR (125MHz, $CDCl_3$): δ 38.72, 71.37, 114.67, 121.79, 125.06, 127.95, 128.50, 128.68, 129.00, 136.20, 138.96, 150.91.

2-Hydroxyphenyl methanesulfonate

2-(Benzyloxy)phenyl methanesulfonate (4.00g, 14.37mmol) was dissolved in dry DCM (50mL) under nitrogen atmosphere. Boron trifluoride diethyl etherate (8.16g, 57.49mmol) was added followed by dimethyl sulfide (3.57g, 57.49mmol) and the reaction mixture was stirred at rt overnight. The reaction mixture was poured onto ice and the aqueous layer was extracted with DCM. The organic layers were combined, washed with water, dried (Na_2SO_4), filtered and evaporated to give the title compund (2.49g, 92%). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.26 (s, 3H), 6.16 (s, 1H), 6.96 (dt, 1H), 7.09 (dd, 1H), 7.22-7.28 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 37.74, 119.01, 121.65, 123.71, 129.09, 136.99, 148.43; Mass Spectrum: M-H$^+$ 187.

tert-Butyl [1-(6-chloropyridin-3-yl)piperidin-4-yl]carbamate

Step1: A solution of 2-chloro-5-fluoropyridine (1.77g, 13.47mmol), tert-butyl piperidine-4-ylcarbamate (3.10g, 15.49mmol) and TEA (2.05mL, 14.81mmol) in DMSO (7mL) was heated at 100°C for 17h, 120°C for 4h and 140°C for 20h.

Step2: A solution of 2-chloro-5-fluoropyridine (1.77g, 13.47mmol), tert-butyl piperidine-4-ylcarbamate (2.83g, 14.14mmol) and TEA (2.05ml, 14.81mmol) in DMSO (7ml) was heated at 140°C for 17h. *tert*-Butyl piperidine-4-ylcarbamate (0.269g, 1.35mmol) was added and the reaction mixture was heated at 140°C for 17h and then at 155°C for 8h and the reaction mixture was cooled to rt.

EtOAc was added to the combined reaction mixtures from step1 and step 2, and the organic phase was washed with water and brine before evaporating to dryness. The residue was purfied using the Biotage Horizon HPFC system eluting with 10-65% EtOAc in petroleum ether (40-60°C) to give the title compound (1.21g, 29%) as a solid. ^{1}H NMR(500MHz, CDCl3): 8.02 (d, 1H), 7.21-7.12 (m, 2H), 4.50 (bs, 1H), 3.64 (bs, 1H), 3.64-3.54 (m, 2H), 2.89 (dt, 2H), 2.12-2.04 (m, 2H), 1.60-1.48 (m, 2H), 1.47 (s, 9H); ^{13}C NMR(CDCl3): 155.3, 146.3, 141.3, 138.1, 126.4, 124.1, 79.8, 48.2, 47.6, 32.2, 28.6; Mass Spectrum: M+H 312

1-(6-Chloropyridin-3-yl)piperidin-4-amine dihydrochloride

A solution of *tert*-butyl [1-(6-chloropyridin-3-yl)-piperidin-4-yl)carbamate (1.211g, 3.88mmol) in HCl in Dioxane (4M, 5mL), THF (5mL) and MeOH (4mL) was stirred at rt for 20h. The reaction mixture was filtered, the residue washed with EtOAc and dried to give the title compound (1.02g, 92%) as a solid; ^{1}H NMR (500MHz, CD_3OD): 8.36 (d, 1H), 7.97 (dd, 1H), 7.68 (d, 1H), 4.05-3.96 (m, 2H), 3.51-3.41 (m, 1H), 3.18 (dt, 2H), 2.24-2.17 (m, 2H),

1.85 (dq, 2H); ^{13}C NMR(CD_3OD): 145.8, 136.7, 133.3, 130.7, 126.5, 47.1, 28.9; Mass Spectrum: M+H 212.

Carbamic acid, [2-[[[3-(difluoromethoxy)phenyl]methyl]amino]-2-oxoethyl]-, 1,1-dimethylethyl ester

N-(*tert*-Butoxycarbonyl)glycine (1.01g, 5.78mmol) was dissolved in dry DMF (12mL) and DIPEA (2.24g, 17.33mmol) was added followed by HOAt (0.87g, 6.35mmol) and EDC (1.44g, 7.51mmol). The reaction mixture was stirred at rt for 30mins followed by addition of [3-(difluoromethoxy)benzyl]amine (1.00g, 5.78mmol). The mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried with Na_2SO_4, filtered and evaporated. The crude product was purified on a Biotage Horizon HPFC system using DCM and MeOH as eluant affording the title compound (1.59g, 83.3%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.84 (d, 2H), 4.47 (d, 2H), 5.27(bs, 1H), 6.52 (t, J_{C-F}=73.6Hz, 1H), 6.75 (bs, 1H), 7.02-7.04 (m, 2H), 7.13 (d, 1H), 7.30-7.34 (m, 1H); Mass Spectrum: M-H$^+$ 329.

N^1-[3-(Difluoromethoxy)benzyl]glycinamide

Carbamic acid, [2-[[[3-(difluoromethoxy)phenyl]methyl]amino]-2-oxoethyl]-, 1,1-dimethylethyl ester (1.58g, 12.62mmol) was dissolved in DCM (6mL) and TFA (5mL) was added. The reaction mixture was stirred at rt for 1h The mixture was concentrated and diluted with EtOAc and washed with saturated aqueous K_2CO_3. The organic layer was dried with Na_2SO_4, filtered and evaporated affording the title compound (1.07g, 97.2%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.49 (bs, 2H), 3.42 (s, 2H), 4.49 (d, 2H), 6.52 (t, J_{C-F}=73.8Hz, 1H), 7.02-7.06 (m, 2H), 7.15 (d, 1H), 7.33 (t, 1H), 7.72 (bs, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 42.70, 44.95, 116.13 (t, J_{C-F}=259.4Hz), 118.52, 118.95, 124.84, 130.29, 141.07, 151.70, 173.01; Mass Spectrum: M+H$^+$ 231.

***tert*-Butyl (1-pyridin-2-ylpiperidin-4-yl)carbamate**

A solution of 2-chloropyridine (0.83ml, 8.81mmol), tert-butyl piperidine-4-ylcarbamate (1.85g, 9.24mmol) and TEA (0.98mL, 9.69mmol) in DMSO (5mL) was heated at 120°C for 4h 45mins and then warmed to 140°C for 2 days. EtOAc was added and the organic phase was washed with water then brine before evaporating to dryness. The residue was purified on a Biotage Horizion HPFC system eluting with 20% EtOAc in petroleum ether (40-60°C) to

give the title compound (0.65mg, 27%). ^{1}H NMR(500MHz, $CDCl_3$): 8.19 (s, 1H), 7.48 (dd, 1H), 6.67 (d, 1H), 6.61 (t, 1H), 4.49 (bs, 1H), 4.21 (d, 2H), 3.70 (bs, 1H), 2.99 (t, 2H), 2.05 (d, 2H), 1.59-1.38 (m, 11H). 13C NMR($CDCl_3$): 159.5, 155.4, 148.2, 137.7, 113.3, 107.5, 79.6, 48.4, 44.6, 32.3, 28.7; Mass Spectrum: M+H 278.

1-Pyridin-2-ylpiperidin-4-amine dihydrochloride

A solution of *tert*-butyl (1-pyridin-2-ylpiperidin-4-yl)carbamate (0.64g, 2.31mmol) in HCl in Dioxane (4M, 3.5ml), THF (2.5ml) and MeOH (2ml) was stirred at rt for 17h. The reaction mixture was filtered, the residue washed with EtOAc and dried to give the title compound (0.49mg, 85%) as a solid. ^{1}H NMR(500MHz, D_2O): 7.91 (dd, 1H), 7.78 (d, 1H), 7.22 (d, 1H), 6.88 (t, 1H), 4.12 (d, 2H), 3.56-3.48 (m, 1H), 3.26 (t, 2H), 2.15 (d, 2H), 1.67 (dq, 2H); ^{13}C NMR(D_2O): 152.1, 144.7, 135.9, 113.3, 47.6, 44.7, 28.8; Mass Spectrum: M+H 178

***tert*-Butyl [1-(5-fluoropyridin-2-yl)piperidin-4-yl]carbamate**

Step1: A solution of 2-chloro-5-fluoropyridine (1.77g, 13.47mmol), *tert*-butyl piperidine-4-ylcarbamate (3.10g, 15.49mmol) and TEA (2.05mL, 14.81mmol) in DMSO (7mL) was heated at 100°C for 17h, 120°C for 4h and 140°C for 20h.

Step2: A solution of 2-chloro-5-fluoropyridine (1.77g, 13.47mmol), tert-butyl piperidine-4-ylcarbamate (2.83g, 14.14mmol) and TEA (2.05mL, 14.81mmol) in DMSO (7mL) was heated at 140°C for 17h. *tert*-Butyl piperidine-4-ylcarbamate (0.269g, 1.35mmol) was added and the reaction mixture heated at 140°C for 17h and then at 155°C for 8h before cooling to rt.

EtOAc was added to the combined reaction mixtures from step1 and step2, and the organic phase was washed with water and brine before evaporating to dryness. The residue was purfied using the Biotage Horizon HPFC system eluting with 10-65% EtOAc in petroleum ether (40-60°C) to give the title compound (0.368g, 9%) as a solid. ^{1}H NMR(500MHz, $CDCl_3$): 8.05 (d, 1H), 7.27-7.20 (m, 1H), 6.64 (dd, 1H), 4.49 (bs, 1H), 4.16-4.04 (m, 2H), 3.68 (bs, 1H), 2.96 (dt, 2H), 2.10-2.00 (m, 2H), 1.56-1.40 (m, 11H); ^{13}C NMR($CDCl_3$): 156.6, 155.4, 154.6, 152.6, 134.9, 134.8, 125.3, 125.1, 108.2, 108.1, 79.7, 48.2, 45.5, 32.3, 28.6; Mass Spectrum: M+H 296.

1-(5-Fluoropyridin-2-yl)piperidin-4-amine dihydrochloride

A solution of *tert*-butyl (1-(5-fluoropyridin-2-yl)piperidin-4-yl)carbamate (0.36g, 1.22mmol) in HCl in Dioxane (4M, 2mL), THF (2mL) and MeOH (2mL) was stirred at rt. After 4h the reaction mixture was filtered, the residue washed with EtOAc and dried to give the title compound (0.31g, 96%) as a solid. ^{1}H NMR(500MHz, CD_3OD): 8.10-8.02 (m, 2H), 7.52 (dd, 1H), 4.34-4.26 (m, 2H), 3.61-3.50 (m,'1H), 3.38 (dt, 2H), 2.28-2.21 (m, 2H), 1.80 (dq, 2H); ^{13}C NMR(CD_3OD): 153.2, 151.2, 151.0, 134.5, 134.3, 123.9, 123.6, 115.0, 114.9, 45.3, 29.1; Mass Spectrum: M+H 196.

tert-Butyl [1-(5-chloropyridin-2-yl)piperidin-4-yl]carbamate

A solution of 2,5-dicholoropyridine (1.00g, 6.78mmol), *tert*-butyl piperidine-4-ylcarbamate (1.42g, 7.06mmol) and TEA (1.03mL, 7.43mmol) in DMSO (5mL) was heated at 120°C for 21h and then to 140°C for 41h. EtOAc was added and the organic phase was washed with water, brine, and evaporated to dryness. The residue was purified using the Biotage Horizon HPFC system eluting with 0-20% EtOAc in DCM to give the title compound (1.16g, 55%) as a solid. ^{1}H NMR (500MHz, $CDCl_3$): 8.10 (d, 1H), 7.41 (dd, 1H), 6.61 (d, 1H), 4.18 (bs, 1H), 4.20-4.12 (m, 2H), 3.70 (m, 2H), 2.99 (dt, 2H), 2.08-1.98 (m, 2H), 1.58-1.38 (m, 11H); ^{13}C NMR($CDCl_3$): 157.8, 155.4, 146.5, 137.4, 120.1, 108.1, 79.7, 48.3, 44.8, 32.2, 28.6; Mass Spectrum: M+H 256.

1-(5-Chloropyridin-2-yl)piperidin-4-amine dihydrochloride

A solution of *tert*-butyl (1-(5-chloropyridin-2-yl)piperidin-4-yl)carbamate (1.15g, 3.70mmol) in HCl in Dioxane (4M, 5mL) and THF (5mL) was stirred at rt for 6.5h. 4M HCl in Dioxane (2mL) was added and the reaction mixture stirred for another 20h. The reaction mixture was filtered, the residue was washed with EtOAc and dried to give the title compound (1.06g, 100%) as a solid. ^{1}H NMR(500MHz, CD_3OD): 8.10 (s, 1H), 8.06 (d, 1H), 7.52 (d, 1H), 4.36 (d, 2H), 3.62-3.54 (m, 1H), 3.42 (dt, 2H), 2.18 (d, 2H), 1.82 (dq, 2H); ^{13}C NMR(CD_3OD): 151.4, 144.4, 134.6, 120.0, 114.7, 45.2, 29.1; Mass Spectrum: M+H 212.

tert-Butyl {1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate

A solution of 2-bromo-4-trifluoromethylpyridine (1.00g, 4.42mmol), *tert*-butyl piperidine-4-ylcarbamate (0.93g, 4.65mmol) and TEA (0.67mL, 4.86mmol) in DMSO (5mL) was heated at 120°C for 17h. The reaction mixture was evaporated to dryness, Et_2O was added, and the organic phase was washed with water, brine and evaporated to dryness. The residue was purified using the Biotage Horizon HPFC system eluting with 22% EtOAc in petroleum ether

(40-60°C) to give the title compound (1.08g, 71%) as a solid. ^{1}H NMR(500MHz, $CDCl_3$): 8.30 (d, 1H), 6.82 (s, 1H), 6.77 (d, 1H), 4.49 (bs, 1H), 4.36-4.22 (m, 2H), 3.74 (bs, 1H), 3.06 (td, 2H), 2.10-2.04 (m, 2H), 1.56-1.38 (m, 11H); ^{13}C NMR($CDCl_3$): 159.4, 155.4, 149.5, 140.1, 139.9, 124.5,122.4, 108.1, 102.7, 79.8, 48.3, 44.4, 32.3, 28.6; Mass Spectrum: M+H 346.

1-[4-(Trifluoromethyl)pyridin-2-yl]piperidin-4-amine

A solution of *tert*-butyl {1-[4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)carbamate (1.07g, 3.09mmol) in HCl in Dioxane (4M, 5mL) and THF (5mL) was stirred at rt for 6.5h. HCl in Dioxane (4M, 2mL) was added and the reaction mixture was stirred for another 20h. The reaction mixture was filtered, the residue washed with EtOAc and dried to give the title compound (0.99g, 100%) as a solid solid. ^{1}H NMR(500MHz, CD_3OD): 8.19 (d, 1H), 7.82 (s, 1H), 7.22 (d, 1H), 4.64 (d, 2H), 3.66-3.56 (m, 1H), 3.52 (td, 2H), 3.29 (d, 2H), 1.87 (dq, 2H); ^{13}C NMR(CD_3OD): 152.6, 144.8, 144.5, 144.2, 143.9, 138.7, 125.3, 123.1, 120.9, 118.7, 111.2, 108.1, 45.3, 29.0; Mass Spectrum: M+H 246

***tert*-Butyl [2-(3-bromophenyl)ethyl]carbamate**

[2-(3-Bromophenyl)ethyl]amine (2.22g, 11.09mmol) was dissolved in dry THF (80mL) and TEA (1.12g, 11.09mmol) was added. The mixture was cooled in an ice-bath. Di-*tert*-butyl dicarbonate (2.42g, 11.09mmol) was added. The reaction mixture was stirred for 1h at 0°C and at rt for 2h. The solvent was evaporated affording the title compound (3.44g, 103%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.79 (t, 2H), 3.37 (q, 2H), 4.58 (bs, 1H), 7.12-7.15 (m, 1H), 7.17-7.20 (m, 1H), 7.35-7.38 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.63, 36.11, 41.82, 79.61, 122.83, 127.71, 129.78, 130.35, 132.12, 141.64, 156.05; Mass Spectrum: M-Na^+ 323.

***tert*-Butyl [2-(3-cyanophenyl)ethyl]carbamate**

tert-Butyl [2-(3-bromophenyl)ethyl]carbamate (0.60g, 1.99mmol) was dissolved in dry DMF (18mL) in a under nitrogen atmosphere. Zinc cyanide (0.47g, 3.99mmol) and tetrakis(triphenylphosphine)palladium (0.18g, 0.16mmol) was added. The reaction mixture was heated in a microwave reactor at 150°C for 20mins. The procedure was repeated two more times with equal amount of starting material and the resulting three mixtures were combined and diluted with EtOAc. The mixture was washed with saturated aqueous $NaHCO_3$

and water, dried with Na_2SO_4, filtered and evaporated. The crude product was purified using Biotage Horizon HPFC system using Heptane and EtOAc as eluant affording the title compound (0.95g, 64.3%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.82 (t, 2H), 3.34 (q, 2H), 4.75 (bs, 1H), 7.37-7.50 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.57, 36.09, 41.63, 79.61, 112.69, 119.05, 129.56, 130.38, 132.57, 133.68, 140.86, 156.06.

3-(2-Aminoethyl)benzonitrile

tert-Butyl [2-(3-cyanophenyl)ethyl]carbamate (0.949g, 3.853mmol) was dissolved in DCM (5mL) and TFA (4mL) and stirred at rt for 2h. The mixture was concentrated and redissolved in EtOAc. The mixture was washed with saturated aqueous K_2CO_3, dried over Na_2SO_4, filtered and evaporated affording the title compound (0.40g, 71.7%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.18 (bs, 2H), 2.79 (t, 2H), 3.00 (t, 2H), 7.39-7.47 (m, 2H), 7.50-7.53 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 39.81, 43.42, 112.74, 119.17, 129.47, 130.24, 132.57, 133.66, 141.67.

4-(Benzyloxy)phenyl methanesulfonate

4-(Benzyloxy)phenol (4.00g, 19.98mmol) was dissolved in dry DCM (80mL) under nitrogen atmosphere and cooled in an ice-water bath. Methanesulfonyl chloride (2.75g, 23.97mmol) was added during stirring followed by TEA (3.03g, 29.96mmol). The reaction mixture was stirred at rt for 2h and then washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated affording the title compund (5.32g, 95.6%). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.13 (s, 3H), 5.08 (s, 2H), 7.01 (m, 2H), 7.23 (m, 2H), 7.35-7.45 (m, 5H).

4-Hydroxyphenyl methanesulfonate

4-(Benzyloxy)phenyl methanesulfonate (5.31g, 19.08mmol) was dissolved in dry DCM (70mL) under nitrogen atmosphere. Boron trifluoride diethyl etherate (10.83g, 76.31mmol) was added followed by dimethyl sulfide (4.74g, 76.31mmol) and the reaction mixture was stirred at rt for 3h. The reaction mixture was poured onto ice and the aqueous layer was extracted with DCM. The organic layers were combined, washed with water, dried over Na_2SO_4, filtered and evaporated to give the title compound (2.96g, 82.5%). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.14 (s, 3H), 5.51 (s, 1H), 6.83 (d, 2H), 7.14 (d, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 37.35, 116.74, 123.49, 142.68, 155.06.

tert-Butyl {1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-yl}carbamate

2,3-Dichloro-5-(trifluoromethyl)pyridine (1.50g, 6.94mmol), *tert*-butyl azetidin-3-ylcarbamate (1.67g, 9.72mmol) and K_2CO_3 (2.88g, 20.83mmol) were dissolved in dry DMF (13mL) under nitrogen atmosphere. The reaction mixture was heated in a microwave reactior at 150°C for 15mins. The reaction mixture was filtered and diluted with EtOAc, washed with water, dried over $MgSO_4$, filtrered and evaporated. The crude product was purified by column chromatography (ISOLUTE SI (20g), eluated with DCM, DCM/MeOH (99:1)) affording the title compound (0.85g, 34.8%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.48 (s, 9H), 4.10-4.14 (m, 2H), 4.57 (bs, 1H), 4.65 (t, 2H), 5.00 (bs, 1H), 7.61 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.56, 41.67, 60.34, 80.45, 115.51, 117.44 (q, J_{C-F}=33.2Hz), 123.83 (m, J_{C-F}=271.4Hz), 135.06, 143.75, 155.18, 157.35; Mass Spectrum: M-H$^+$ 350.

1-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-amine

tert-Butyl {1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-yl}carbamate (0.85g, 2.42mmol) was dissolved in DCM (4mL) and TFA (3mL) and stirred at rt for 1h. The mixture was concentrated and redissolved in EtOAc, washed with saturated aqueous K_2CO_3. The organic layer was dried with Na_2SO_4, filtered and evaporated affording the title compound (0.58g, 95.1%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.65 (bs, 2H), 3.91-3.98 (m, 3H), 4.57-4.61 (m, 2H), 7.58 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 43.68, 63.02, 115.38, 116.90 (q, J_{C-F}=33.2Hz), 123.91 (q, J_{C-F}=270.9Hz), 134.95, 143.76, 157.56; Mass Spectrum: M+H$^+$ 252.

Carbamic acid, [2-oxo-2-[(phenylmethyl)amino]ethyl]-, 1,1-dimethylethyl ester

N-(*tert*-Butoxycarbonyl)glycine (1.64g, 9.33mmol) was dissolved in dry DCM (20mL) and DIPEA (3.62g, 27.99mmol) was added followed by HOAt (1.40g, 10.27mmol) and EDC (2.33g, 12.13mmol). The reaction mixture was stirred at rt for 30mins and benzylamine (1.00g, 9.33mmol) was added. The mixture was stirred at rt overnight. The reaction mixture was concentrated and diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried with Na_2SO_4, filtered and evaporated. The crude product was purified on a Biotage Horizon HPFC system using DCM and MeOH as eluant affording the title compound (1.26g, 51%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.82 (d, 2H), 4.44 (d, 2H), 5.35 (bs, 1H), 6.73 (bs, 1H), 7.25-7.28 (m, 3H), 7.30-7.34 (m, 2H); Mass Spectrum: M+H$^+$ 265.

N^1-Benzylglycinamide

Carbamic acid, [2-oxo-2-[(phenylmethyl)amino]ethyl]-, 1,1-dimethylethyl ester (1.25g, 12.62mmol) was dissolved in DCM (6mL) and TFA (5mL) was added. The reaction mixture was stirred at rt for 2h. The mixture was concentrated and diluted with EtOAc and washed with saturated aqueous K_2CO_3. The organic layer was dried with Na_2SO_4, filtered and evaporated affording the title compound (0.73g, 94.5%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.48 (bs, 2H), 3.38 (s, 2H), 4.46 (d, 2H), 7.26-7.35 (m, 5H), 7.64 (bs, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 43.24, 45.00, 127.65, 127.99, 128.90, 138.66, 172.93; Mass Spectrum: $M+H^+$ 165.

tert-Butyl (4-hydroxycyclohexyl)carbamate

4-Aminocyclohexanol (5.00g, 43.41mmol) was dissolved in dry THF (250mL) and TEA (4.39g, 43.41mmol) was added. The mixture was cooled in an ice-bath. Di-_tert_-butyl dicarbonate (9.47g, 43.41mmol) was added and the reaction mixture was stirred at 0°C for 1h and left overnight at rt. The solvent was evaporated and column chromatography of the crude product (ISOLUTE SI (20g) Heptane/EtOAc; 90:10-70:30) afforded the title comound (6.13g, 65.6%) as a mixture of cis and trans isomeres. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.21-1.37 (m, 4H), 1.45 (d, 9H), 1.53 (s, 9H), 1.57-1.73 (m, 8H), 1.88-1.96 (m, 4H), 3.25-3.31 (m, 1H), 3.40 (bs, 1H), 3.48-3.54 (m, 1H), 3.80-3.84 (m, 1H).

4-[(_tert_-Butoxycarbonyl)amino]cyclohexyl methanesulfonate

tert-Butyl (4-hydroxycyclohexyl)carbamate (2.5g, 11.61 mmol) and TEA (3.23 ml, 23.22 mmol) was dissolved in DCM (50 ml) and cooled to 0°C with an icebath. Methansulfonyl chloride (1.17 ml, 15.10 mmol) was added dropwise and the icebath was removed. After stirring at rt for 2 h the reaction mixture was washed with water (200 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography using a 70:30 mixture of heptane:EtOAc to give the title compound (1.8g, 53%) as 50:50 mixture of cis and trans isomers. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.91-4.83 (m, 1H), 4.67-4.56 (m,1H), 4.53-4.31 (m, 2H), 3.58-3.36 (m, 2H), 3.00(ds, 6H), 2.17-1.98 (m, 6H), 1.88-1.78 (m, 2H), 1.77-1.50 (m, 6H), 1.43 (ds, 18H), 1.33-1.18 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 155.4, 79.9, 78.1, 48.2, 39.0, 38.9, 31.3, 30.8, 30.0, 28.6, 27.7.

tert-Butyl (4-{[4-(trifluoromethyl)phenyl]thio}cyclohexyl)carbamate

4-[(*tert*-Butoxycarbonyl)amino]cyclohexyl methanesulfonate (0.7g, 2.39 mmol), 4-(trifluoromethyl)thiophenol (1.28g, 7.16 mmol) and K_2CO_3 (1.32g, 9.54 mmol) was dissolved in THF (21 ml) and the reaction mixture was heated in a microwave reactor at 130°C for 30mins. The reaction mixture was diluted with water (300 ml) and extracted with EtOAc (2x150 ml). The combined organic phases were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by silica gel column chromatography using a 85:15 mixture of heptane:EtOAc to give the title compound (0.386g, 43%) as a 50:50 mixture of cis and trans isomers. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.55-7.50 (m, 4H), 7.45-7.40 (m, 4H), 4.70-4.23 (m, 2H), 3.69-3.36 (m, 3H), 3.16-3.05 (m, 1H), 2.13-2.04 (m, 4H), 1.95-1.64 (m, 9H), 1.54-1.40 (m, 1H), 1.45 (ds, 18H), 1.30-1.15 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 155.4, 141.1, 140.7, 130.5, 129.9, 128.6, 128.5, 128.2, 126.0, 125.9, 125.9, 125.9, 125.4, 123.2, 79.5, 49.1, 47.9, 44.8, 43.8, 33.4, 32.0, 29.2, 29.1, 28.6 .

(4-{[4-(Trifluoromethyl)phenyl]thio}cyclohexyl)amine

tert-Butyl (4-{[4-(trifluoromethyl)phenyl]thio}cyclohexyl)carbamate (0.38g, 1.01 mmol) was dissolved in THF:MeOH 8:2 (10 ml) and HCl in 1,4-dioxane (4M, 2 ml) was added. The reaction mixture was stirred at rt for 15h, and then evaporated. The crude product was diluted with EtOAc (100ml), washed with a mixture of saturated aqueous Na_2CO_3 and water (1:2, 100 ml) and water (2x100 ml). The organic layer was dried over Na_2SO_4, filtrated and evaporated to yield the title compound (0.27g, 97%) as a 50:50 mixture of cis and trans isomers. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.56-7.48 (m, 4H), 7.46-7.39 (m, 4H), 3.59-3.52 (m, 1H), 3.17-3.07 (m, 1H), 2.90-2.79 (m, 1H), 2.78-2.68 (m, 1H), 2.13-2.03 (m, 2H), 1.99-1.14 (m, 18H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 141.6, 141.0, 130.2, 129.7, 125.9, 125.9, 50.0, 48.9, 45.0, 44.0, 36.6, 32.3, 32.1, 30.5, 29.2, 29.0, 28.6.

***tert*-Butyl {1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate**

Mixture of 2-chloro-5-(trifluoromethyl)pyridine (1.00g, 5.51mmol), *tert*-butyl 4-aminopiperidine-1-carboxylate (1.16g, 5.78mmol) and TEA (0.84ml, 6.06mmol) in DMSO (5ml) was heated at 120°C for 18h. The mixture was evaporated, EtOAc was added and the mixture was washed with water, then brine and evaporated to dryness. The crude product was purified by triturating with MeOH and then EtOAc to give the title compound (1.29g, 67%) as a solid. ^{1}H-NMR (500MHz $CDCl_3$): 8.39 (s, 1H), 7.62 (dd, 1H), 6.66 (d, 1H), 4.48 (bs, 1H), 4.38-4.28 (m, 2H), 3.75 (bs, 1H), 3.07 (dt, 2H), 2.10-2.02 (m, 2H), 1.58-1.38 (m, 11H); ^{13}C-

NMR (125MHz $CDCl_3$): 160.3, 155.3, 146.0, 134.8, 125.9, 123.8, 115.3, 115.0, 105.8, 79.8, 48.3, 44.1, 32.3, 28.6; Mass Spectrum $M+H^+$ 346.

1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-amine dihydrochloride

A mixture of *tert*-butyl {1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate (1.27g, 3.68mmol) in HCl in Dioxane/THF (4M, 1:1; 10ml) was stirred at rt. After 6.5h more HCl in Dioxane (4M, 2ml) was added and the resulting mixture stirred for a further 18h. The mixture was filtered and the residue was washed with EtOAc to give the title compound (1.04g, 89%) as a solid. ^1H NMR (500MHz CD_3OD): 8.35 (s, 1H), 8.20 (dd, 1H), 7.60 (d, 1H), 4.46 (d, 2H), 3.66-3.56 (m, 1H), 3.48 (td, 2H), 2.28 (d, 2H), 1.90-1.80 (m, 2H); ^{13}C NMR (125MHz CD_3OD): 153.5, 139.2, 136.3, 126.1, 123.9, 121.8, 120.0, 116.2, 115.9, 115.6, 115.3, 113.9, 45.2, 29.1; Mass Spectrum: $M+H^+$ 246.

***tert*-Butyl 3-(cyanomethoxy)azetidine-1-carboxylate**

NaH (60% dispersion in mineral oil, 276mg, 6.89mmol) was added to an ice cold solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (0.92mg, 5.30mmol) in THF (8mL) and stirred for 15mins. Bromoacetonitrile (0.52mL, 7.43mmol) was added dropwise and the reaction mixture allowed to warm to room temperature. After 2.5h, bromoacetonitrile (0.074mL, 1.06mmol) was added and the reaction mixture stirred at rt. After 17h, NaH (60% dispersion in mineral oil, 0.085mg, 2.12mmol) and bromoacetonitrile (0.074mL, 1.06mmol) were added. After 2h the reaction mixture was evaporated to dryness and the crude product purified on a Biotage Horizon HPFC system eluting with 5-90% EtOAc in petroleum ether (40-60°C) to give the title compound (0.47g, 42%) as an oil. ^1H NMR($CDCl_3$): δ 4.46-4.40 (m, 1H), 4.24 (s, 2H), 4.17 (dd, 2H), 3.92 (dd, 2H), 1.45 (s, 9H); ^{13}C NMR(CDCl3): δ 156.3, 115.6, 80.2, 69.3, 56.3, 54.6, 28.6.

***tert*-Butyl 3-(2-aminoethoxy)azetidine-1-carboxylate**

A mixture of *tert*-butyl 3-(cyanomethoxy)azetidine-1-carboxylate (0.46g, 2.19 mmol) and 10% Pd/C (10%) in EtOH was stirred under H_2 gas at 3atm. After 3h the reaction mixture was filtered through celite and the filtrate evaporated to dryness to give the title compound (0.41g, 87%) as an oil. ^1H NMR($CDCl_3$): δ 4.27-4.20 (m, 1H), 4.08 (t, 2H), 3.84 (dd, 2H), 3.49 (t, 2H), 2.84 (t, 2H), 1.45 (s, 9H); ^{13}C NMR(CDCl3): δ 156.6, 79.7, 68.3, 68.2, 56.7, 49.4, 28.6.

2-[4-(Trifluoromethoxy)phenyl]acetamide

4-(Trifluoromethoxy)phenylacetic acid (2 g, 9.085 mmol) was dissolved in DMF (20 ml, dry) and PyBOP (4.728 g, 9.085 mmol) was added. The mixture was stirred in an ice-bath and ammonia gas was bubbled in for 5 mins. The ice-bath was removed and the mixture was stirred at rt overnight and then evaporated in vacuum. Water (50 ml) was added into the residue and it was extracted with EtOAc (20 ml x3). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (15 ml), water (20 ml x3), brine (15 ml), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (ISOLUTE SI, 20g/70 ml), eluting with DCM, then MeOH/DCM (1:99), to give the title compound (1.14 g, 57%) as a white solid. Mass Spectrum: M-H^+ 218. ^{1}H NMR (400 MHz, CD_3OD): δ 3.53 (s, 2H), 7.20 (d, 2H), 7.38 (d, 2H). ^{13}C NMR (100 MHz, CD_3OD): 42.5, 121.9 (q, J=253 Hz), 122.1, 131.8, 136.3, 149.4, 176.2.

2-[4-(Trifluoromethoxy)phenyl]ethanamine

2-[4-(Trifluoromethoxy)phenyl]acetamide (1.13 g, 5.156 mmol) was dissolved in THF (20 ml) and the reaction mixture was cooled in an ice-bath. Borane dimethyl sulfide complex (6.4 ml, 2M in THF) was added dropwise. After the addition, the cooling-bath was removed and the mixture was heated to reflux for 5 h and cooled down to rt. HCl (10 %, 4 ml) was added, the mixture was stirred at rt overnight and then evaporated to remove THF. Water (15 ml) and diethyl ether (15 ml) were added into the residue. The two phases were separated and $NaHCO_3$ (sat.) was added into the water phase. It was then extracted with EtOAc (20 ml x3). The extracts were combined and washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (ISOLUTE SI, 20g/70 ml), eluting with MeOH/DCM (1:99, 2:98, 5:95 then 10:90), to give 0.2 g desired product and 0.46 g mixture. The mixture was further purified by re-chromatography (ISOLUTE SI, 20g/70 ml), eluting with MeOH/EtOAc (2:98, 5:95, 10:90), to give 0.107g more of the desired product. In total (0.307g, 29%) of the title compound was obtained. Mass Spectrum: M+H^+ 206. ^{1}H NMR (400 MHz, CD_3OD): δ 2.95 (t, 2H), 3.12 (t, 2H), 7.23 (d, 2H), 7.38 (d, 2H). ^{13}C NMR (100 MHz, CD_3OD): 35.3, 42.5, 122.2 (q, J=250 Hz), 122.6, 131.7, 136.2, 149.7.

***Tert*-Butyl-(2-{[5-(trifluoromethyl)pyridine-2-yl]oxy}-ethyl)carbamate**

Tert-Butyl (2-hydroxyethyl)carbamate (8.88g, 55.08mmol) was added to a solution of NaH (55%, 55.08mmol, washed twice with petroleum ether) in DMF (150ml) at -10°C and stirred

for 10mins. 2-Chloro-5-(trifluoromethyl)pyridine (10.0g, 55.08mmol) was added and the rection mixture was stirred at rt for 3 days, heated to 100°C and cooled to rt. The reaction mixture was evaporated, the residue was washed with isopropylether, and the solution was decanted from insoluble salts and concentrated. The residue was dissolved in EtOAc, washed twice with water, dried over $MgSO_4$ and concentrated. Recrystallisation from isobutylethyl ether gave the title compound (6.2g, 37%). ^{1}H-NMR (500MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.56 (br.m, 2H), 4.45 (t, 2H), 6.84 (d, 1H), 7.79 (dd, 1H), 8.44 (s, 1H.

2-{[5-Trifluoromethyl)pyridine-2-yl]oxy}ethyl)amine hydrochloride

tert-Butyl-(2-{[5-(trifluoromethyl)pyridine-2-yl]oxy}-ethyl)carbamate (6.1g, 19.92mmol) in EtOAc (saturated with HCl) was stirred for 2 days. The reaction mixture was concentrated enough for precipitation of the title compound (4.7g) as the HCl-salt. ^{1}H-NMR (300MHz, CD_3OD): δ 3.39 (t, 2H), 4.64 (t, 2H), 7.04 (d, 1H), 7.99 (dd, 1H), 8.5 (s, 1H).

***tert*-Butyl (1-pyridin-2-ylazetidin-3-yl)carbamate**

The title compound was prepared from 2-chloropyridine and *tert*-butyl azetidin-3-ylcarbamate in a similar manner as described for *tert*-butyl {1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-yl}carbamate. ^{1}H NMR (500MHz $CDCl_3$): δ 1.46 (s, 9H), 3.76-3.80 (m, 2H), 4.31-4.35 (m, 2H), 4.63 (bs, 1H), 5.10 (bs, 1H), 6.29 (d, 1H), 6.61-6.64 (m, 1H), 7.43-7.47 (m, 1H), 8.14-8.16 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 28.58, 41.79, 58.58, 80.22, 106.36, 113.48, 137.37, 148.42, 155.24, 160.66; Mass Spectrum: $M+H^+$ 250.

1-Pyridine-2-ylazetidin-3-amine

The title compound was prepared from *tert*-butyl (1-pyridin-2-ylazetidin-3-yl)carbamate in a similar manner as described for 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-amine. ^{1}H NMR (500MHz $CDCl_3$): δ 1.96 (bs, 2H), 3.59-3.63 (m, 2H), 3.89-3.95 (m, 1H), 4.22-4.27 (m, 2H), 6.26 (d, 1H), 6.55-6.58 (m, 1H), 7.38-7.43 (m, 1H), 8.11 (s, 1H).

2,6-Dimethylphenyl 4-[(*tert*-butoxycarbonyl)amino]butanoate

2,6-Dimethylphenol (0.257 g, 2.1 mmol) and 4-[(*tert*-butoxycarbonyl)amino]butanoic acid (0.427 g, 2.1 mmol) were dissolved in THF (10 ml, dry) and DMAP (0.005 g, 0.04 mmol) was added. After cooling down to 0-2 °C, EDC (0.483 g, 2.52 mmol) was added portionwise under nitrogen atmosphere. The ice bath was removed and stirring was continued over night

at rt. After 17 h, the mixture was diluted with DCM (50 ml) and extracted with water (20 ml), HCl (2N, 20 ml) and water (20 ml) again. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel, using DCM / MeOH (95:5) as eluent, to give the title compound (0.493 g, 76%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (s 9H), 1.94-2.01 (m, 2H), 2.14 (s, 6H), 2.66 (t, 2H), 3.24-3.29 (m, 2H), 4.66 (bs, 1H), 7.05 (s, 3H); Mass Spectrum: M-*tert*-Bu + H^+ 252.1

2,6-Dimethylphenyl 4-aminobutanoate hydrochloride

2,6-Dimethylphenyl 4-[(*tert*-butoxycarbonyl)amino]butanoate (0.49 g, 1.594 mmol) was dissolved in DCM (20 ml) and HCl (4M in dioxane, 1.2 ml) was added dropwise at 0 °C. The mixture was stirred for 30 minutes at 0-2 °C before the ice bath was removed and stirring was continued at rt. The mixture was evaporated in vacuum to give the title compound (0.371 g, 86%) as a white solid. It was used without further purification. ^1H NMR (400 MHz, DMSO-d6): δ 1.88-1.96 (m, 2H), 2.07 (s, 6H), 2.80 (t, 2H), 2.85(bs, 2H), 7.02-7.11 (m, 3H), 8.10 (bs, 3H).

Phenyl *N*-(*tert*-butoxycarbonyl)-β-alaninate

The title compound was prepared from *N*-(*tert*-butoxycarbonyl)-β-alanine and phenol in a similar manner as described for 2,6-dimethylphenyl 4-[(*tert*-butoxycarbonyl)amino]butanoate. Mass Spectrum (M-*tert*-Bu) + H^+ 211.09.

Phenyl β-alaninate hydrochloride

The title compound was prepared from phenyl *N*-(*tert*-butoxycarbonyl)-β-alaninate in a similar manner as described for 2,6-dimethylphenyl 4-aminobutanoate hydrochloride. ^1H NMR (400 MHz, CDCl3): δ 7.36-7.40 (t, 2H), 7.22-7.25 (t, 1H), 7.12-7.14 (d, 2H), 4.82 (s, 3H), 3.27-3.30 (m, 2H), 2.99-3.03 (t, 2H).

4-(Trifluoromethoxy)phenyl *N*-(*tert*-butoxycarbonyl)-β-alaninate

The title compound was prepared from *N*-(*tert*-butoxycarbonyl)-β-alanine and 4-(trifluoromethoxy)phenol in a similar manner as described for 2,6-dimethylphenyl 4-[(*tert*-butoxycarbonyl)amino]butanoate. Mass Spectrum (M-*tert*-Bu) + H^+ 293.96

4-(Trifluoromethoxy)phenyl β-alaninate

The title compound was prepared from 4-(trifluoromethoxy)phenyl *N*-(*tert*-butoxycarbonyl)-β-alaninate in a similar manner as described for 2,6-dimethylphenyl 4-aminobutanoate hydrochloride. Mass Spectrum M + H^+ 251.10

1-Methylpiperidin-4-yl *N*-(*tert*-butoxycarbonyl)-β-alaninate

The title compound was prepared from 1-methylpiperidin-4-ol and *N*-(*tert*-butoxycarbonyl)-β-alanine in a similar manner as described for 2,6-dimethylphenyl 4-[(*tert*-butoxycarbonyl)amino]butanoate. ^{1}H NMR (400 MHz, CDCl3): δ 4.99 (s, 1H), 4.74-4.79 (m, 1H), 3.32-3.6 (m, 2H), 2.58 (s, 2H), 2.45-2.49 (t, 2H), 2.23 (s, 3H), 2.16-2.19 (m, 2H), 1.83-1.88 (m, 2H), 1.62-1.71 (m, 2H), 1.34 (s, 9H).

1-Methylpiperidin-4-yl β-alaninate hydrochloride

The title comound was prepared from 1-methylpiperidin-4-yl *N*-(*tert*-butoxycarbonyl)-β-alaninate in a similar manner as described for for 2,6-dimethylphenyl 4-aminobutanoate hydrochloride. Mass Spectrum M + H^+ 188.17.

Mesitylacetaldehyde

2-Mesitylethanol (0.99g, 6.0mmol) was dissolved in DCM (10.0mL, dry) and cooled to 0°C. 1,1,1-Tris(acetyloxy)-1λ^5,2-benziodoxol-3(1*H*)-one (Dess-Martin periodinane) in DCM (15 wt %, 2.80g, 6.60mmol) was added dropwise over a period of 20 mins. The ice bath was removed and the reaction mixture was stirred at rt for 4h. NaOH (2N, 5mL) was added to the mixture and it was diluted with water (5mL). The layers were separated and the organic layer was washed with water, dried over Na2SO4, and evaporated. The residue was purified by column chromatography on silica gel using heptane and EtOAc as eluant giving the title compound (0.69g, 71%). ^{1}H NMR ($CDCl_3$, 400MHz) δ 9.68-9.65 (m, 1H), 6.94-6.90 (m, 2H), 3.75-3.71 (m, 2H), 2.29 (s, 3H), 2.27 (s, 6H).

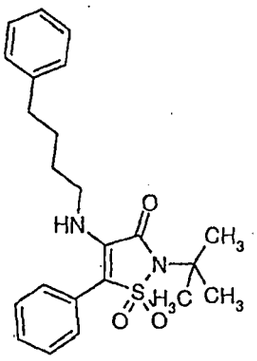
1-Mesitylpropan-2-ol

Mesitylacetaldehyde (0.68g, 4.19mmol) was dissolved in THF (5.0mL, dry) and MeMgBr in Et_2O (3.0M, 0.75g, 6.29mmol)) was added slowly at 0°C. The cooling bath was removed and the reaction mixture was stirred at rt for 4.5h. The mixture was cooled to 0°C and excess Grignard reagent was hydrolyzed with HCl (1N). The mixture was diluted with water and extracted with Et_2O. The organic layer was dried over Na_2SO_4, evaporated and the residue

was purified by column chromatography on silica gel using MTBE, heptane and DCM as eluant giving the title compound (0.51g, 61%). ^{1}H NMR ($CDCl_3$, 500MHz) δ 6.88-6.85 (m, 2H), 4.08-3.99 (m, 1H), 2.87-2.72 (m, 2H), 2.32 (s, 6H), 2.26 (s, 3H), 1.29 (d, 3H).

Example 1

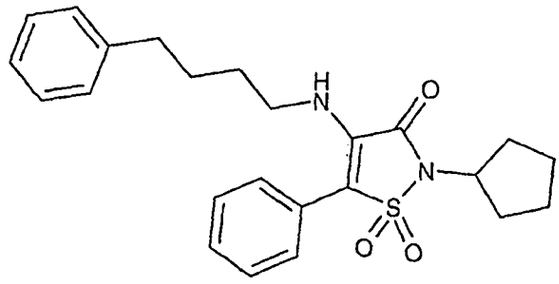
2-*tert*-Butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide



A solution of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.150g, 0.50mmol), TEA (0.076g, 0.751mmol) and 4-phenylbutylamine (0.097g, 0.65mmol) in MeCN (3mL) was heated in a microwave reactor at 120°C for 10 mins. The mixture was evaporated and the residue was purified by silica gel column chromatography using a 85:15 mixture of heptane and EtOAc as eluant, to give the title compound (0.19g, 92%) as a solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.47 (m, 2H), 7.45-7.40 (m, 3H), 7.31-7.26 (m 2H), 7.22-7.17 (m, 1H), 7.08 (d, 2H), 5.26 (t, 1H), 2.88-2.81 (m, 2H), 2.49-7.43 (m 2H), 1.75 (s 9H), 1.48-1.36 (m 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 141.8, 135.3, 131.9, 129.8, 128.8, 128.6, 128.5, 126.2, 125.3, 107.0, 61.7, 44.1, 35.5, 29.2, 28.4, 27.9; Mass Spectrum: M-H$^+$ 413.

Example 2

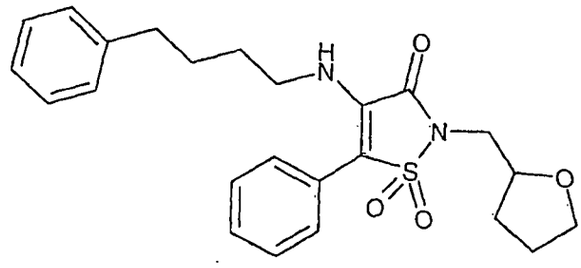
2-Cyclopentyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide



2-*tert*-Butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide (Example 1) (0.150g, 0.364mmol) was dissolved in TFA (3mL) and heated in a microwave reactor at 120°C for 20 mins. TFA was removed in vacuo and the residue was coevaporated with DCM two times. The residue was dissolved in MeCN (3mL) and it was mixed with bromocyclopentan (0.162g, 1.09mmol) and TEA (0.110g, 1.09mmol) and the mixture was heated in a microwave reactor at 120°C for 20 mins, at 160°C for 85 mins and at 170 °C for 20 mins. The residue was purified by column chromatography (Horizons Biotage) using a 90:10 mixture of hexane and EtOAc as eluant, to give the title compound (0.055 g, 36%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.48 (m, 2H), 7.46-7.41 (m, 3H), 7.31-7.25 (m 2H), 7.22-7.18 (m, 1H), 7.10-7.06 (m, 2H), 5.30-5.24 (br m, 1H), 4.41-4.35 (m, 1H), 2.90-2.83 (m 2H), 2.49-2.43 (m 2H), 2.25-2.17 (m 2H), 2.18-2.09 (m 2H), 1.97-1.87 (m 2H), 1.69-1.60 (m 2H), 1.44-1.36 (m 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 141.8, 135.6, 131.8, 129.8, 128.8, 128.6, 128.5, 126.2, 125.3, 106.7, 55.2, 44.2, 35.4, 29.5, 29.2, 28.3, 24.3.

Example 3

5-Phenyl-4-[(4-phenylbutyl)amino]-2-(tetrahydrofuran-2-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

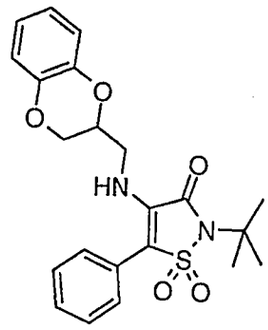


2-*tert*-Butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide (Example 1) (0.150g, 0.364mmol) was dissolved in TFA (3mL) and heated in a microwave reactor at 120°C for 20 mins. TFA was removed in vacuo and coevaporated with DCM two times. The residue was dissolved in MeCN (3mL) and mixed with 2-(bromomethyl)tetrahydrofuran (0.312g, 1.892mmol), TEA (0.148g, 1.454mmol) and K_2CO_3 (0.251g, 1.818mmol) and heated in a microwave reactor at 140°C for 15mins and at 160 °C for 80 mins. The residue was purified by column chromatography (Horizons Biotage) using a 75:25 mixture of hexane and EtOAc as eluant, to give the title compound (0.055g, 36%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H), 7.46-7.41 (m, 3H), 7.31-7.25 (m 2H), 7.22-7.18 (m, 1H), 7.10-7.06 (m, 2H), 5.30-5.24 (br m, 1H), 4.42-4.36 (m, 1H), 4.00-3.95 (m 1H), 3.86-3.79 (m 2H), 3.72-3.65

(dd 1H), 2.91-2.83 (m 2H), 2.49-2.43 (m 2H), 2.14-2.06 (m 1H), 2.06-1.89 (dm 2H), 1.77-1.68 (m 1H), 1.44-1.36 (m 4H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 141.7, 135.6, 131.9, 129.9, 128.8, 128.6, 128.5, 126.2, 125.1, 107.0, 68.5, 44.2, 35.4, 29.6, 29.2, 28.3, 25.7; Mass Spectrum: M-H$^+$ 425.

Example 4

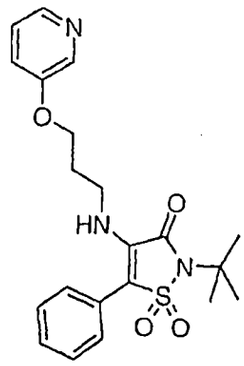
2-*tert*-Butyl-4-[(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide



A mixture of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.150g, 0.50mmol) and (2,3-dihydro-1,4-benzodioxin-2-ylmethyl)amine (0.083g, 0.50mmol) and TEA (0.07mL, 0.50mmol) in MeCN (2mL) was heated in a microwave reactor at 100°C for 45 mins. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography using a 15-25% EtOAc in petroleum ether mixture as eluant, to give the title compound (0.139g, 65%) as a solid; ^{1}H NMR (500 MHz, CDCl3): δ 7.54-7.50 (m, 2H), 7.50-7.45 (m, 3H), 6.92-6.82 (m, 4H), 5.65 (t, 1H), 4.12-4.04 (m, 1H), 3.86 (dd, 1H), 3.68 (dd, 1H), 3.17 (t, 2H), 1.75 (s, 9H); ^{13}C NMR (125 MHz, CDCl3): δ 159.5, 142.9, 142.3, 135.1, 131.7, 130.2, 129.2, 124.8, 122.2, 122.1, 117.7, 117.5, 108.7, 71.4, 65.3, 61.9, 44.1, 27.9; Mass Spectrum: [M+H]$^+$ 429.

Example 5

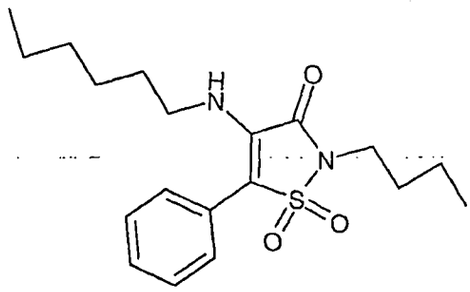
2-*tert*-Butyl-5-phenyl-4-{[3-(pyridin-3-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide



A mixture of 4-[(3-bromopropyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.120g, 0.29mmol), 3-hydroxypyridine (0.028g, 0.29mmol) and K_2CO_3 (0.207g, 1.49mmol) in MeCN (2mL) was heated in a microwave reactor at 140°C for 30 mins. The solvent was evaporated and the residue was purified by silica gel column chromatography using a 35-85% EtOAc in hexane mixture as eluant, to give the title compound (0.056g, 45%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28-8.22 (m, 2H), 7.54-7.50 (m, 2H), 7.50-7.42 (m, 3H), 7.24-7.20 (m, 1H), 7.16-7.12 (m, 1H), 5.68 (t, 1H), 3.92 (t, 2H), 3.14-3.08 (m, 2H), 1.90-1.82 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 154.7, 142.8, 137.9, 135.2, 131.8, 129.9, 128.8, 125.2, 124.1, 121.3, 107.5, 66.3, 61.8, 42.1, 29.0, 27.8; Mass Spectrum: $M+H^+$ 416.

Example 6

2-Butyl-4-(hexylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

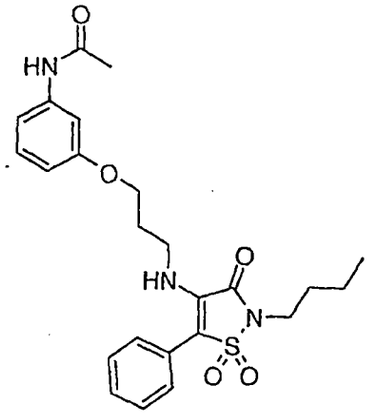


A solution of 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.110g, 0.33mmol) and hexylamine (0.100g, 0.984mmol) in DMF (0.5mL) was heated in a microwave reactor at 140°C for 25 mins. The residue was purified by preparative HPLC (Ace C8 column, 0.1M NH_4OAc/MeCN, gradient) to give the title compound (0.060g, 47%); ^{1}H-NMR (400 MHz, CD_3CN): δ 7.49-7.53 (m, 5H), 5.85 (bs, 1H), 3.66 8(t, 2H), 2.85 (dd, 2H), 1.71-1.80 (m, 2H),

1.37-1.48 (m, 2H), 1.13-1.34 (m, 4H), 0.94-1.09 (m, 7H), 0.82 (t, 3H); Mass Spectrum: M+H 365.

Example 7

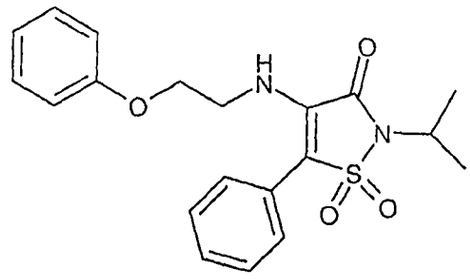
***N*-(3-{3-[(2-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide**



A mixture of 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.150g, 0.50mmol) and 3-(3-aminopropyloxy)acetanilide (0.208mg, 1.00mmol) in MeCN (2mL) was heated in a microwave reactor at 120°C for 15 mins. The reaction mixture was filtered and the solid residue was washed with EtOAc. The filtrate was evaporated and the residue was purified by silica gel column chromatography using a 50-100 % EtOAc in petroleum ether mixture as eluant, to give the title compound (0.148g, 63%) as a solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.52 (m, 2H), 7.50-7.44 (m, 3H), 7.22 (t, 1H), 7.18 (br s, 1H), 6.96 (dd, 1H), 7.64 (dd, 1H), 5.82 (t, 1H), 3.92 (t, 2H), 3.72 (t, 2H), 3.18-3.06 (m, 2H), 2.20 (s, 3H), 1.88-1.80 (m, 4H), 1.50-1.40 (m, 2H), 0.98 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 159.2, 159.0, 139.6, 135.8, 131.7, 130.0, 129.0, 128.9, 125.0, 112.4, 110.8, 106.1, 66.2, 42.7, 40.4, 30.5, 28.9, 25.2, 20.3, 13.8; Mass Spectrum: $[M+H]^+$ 472.

Example 8

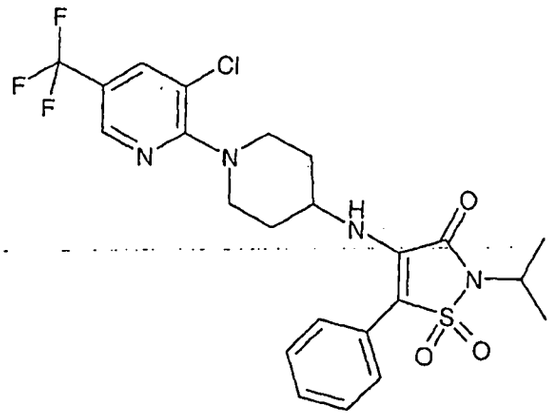
2-Isopropyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide



A solution of 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.200g, 0.700mmol), TEA (0.106g, 1.050mmol) and 2-phenoxyethylamine (0.144g, 1.050mmol) in MeCN (3mL) was heated at in a microwave reactor 120°C for 5 mins. The residue was purified by silica gel column chromatography (Horizons Biotage) using a 65:35 mixture of heptane and EtOAc as eluant to give the title compound (0.262g, 97%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.49-7.45 (m, 3H), 7.32-7.27 (m, 2H), 7.02-6.97 (m, 1H), 6.86-6.83 (m, 2H), 5.71-5.66 (br m, 1H), 4.46-4.39 (m, 1H), 3.89 (t 2H), 3.27 (q 2H), 1.60 (d 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 158.2, 135.6, 131.7, 130.0, 129.8, 129.1, 125.1, 121.8, 114.7, 108.0, 65.8, 47.8, 43.6, 20.4; Mass Spectrum: M-H$^+$ 387.

Example 9

4-({1-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

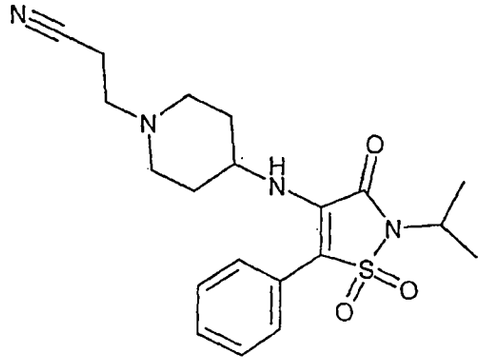


A solution of 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.200g, 0.700mmol), TEA (0.106g, 1.050mmol) and 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-amine (0.294g, 1.050mmol) in MeCN (mL) was heated in a microwave reactor at 120°C for 30 mins. The residue was purified by silica gel column chromatography (Horizons Biotage) using a 1:1 mixture of heptane and EtOAc as eluant, to give the title compound (0.344 g, 93 %); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34-8.33 (m, 1H), 7.74-7.72 (m,

1H), 7.57-7.54 (m, 2H), 7.49-7.46 (m, 3H), 5.27 (d, 1H), 4.47-4.39 (m, 1H), 3.85-3.78 (m, 2H), 3.24-3.14 (m 1H), 2.55-2.48 (m 2H), 1.82-1.76 (m 2H), 1.60 (d 6H), 1.56-1.48 (m 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 158.7, 143.1, 136.2, 134.5, 131.8, 130.2, 129.0, 125.3, 121.3, 120.6, 120.3, 107.1, 66.1, 50.3, 47.9, 47.4, 32.4, 20.4; Mass Spectrum: M-H$^+$ 529.

Example 10

3-{4-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}propanenitrile



A solution of 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.200g, 0.700mmol), TEA (0.283g, 2.800mmol) and 3-(4-aminopiperidin-1-yl)propanenitrile (0.161g, 1.050mmol) in DMF (3mL) was heated in a microwave reactor at 120°C for 10 mins. Water was added and the mixture was extracted with EtOAc. The organic phase was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using a mixture of heptane and EtOAc (20:80) to 100% EtOAc, then a mixture of MeOH and EtOAc (1:99) as eluant, to give the title compound (0.25g, 89%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H), 7.49-7.44 (m, 3H), 5.20 (br d 1H), 4.46-4.38 (m, 1H), 3.01-2.91 (br m, 1H), 2.70-2.65 (br m, 2H), 2.55 (t, 2H), 2.41(t 2H), 1.74-1.63 (m 4H), 1.60 (d 6H) 1.44-1.35 (m 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 134.5, 131.8, 130.1, 128.9, 125.3, 118.8, 106.8, 53.3, 51.5, 50.0, 47.8, 32.4, 20.4, 16.4: Mass Spectrum: M-H$^+$ 403.

Example 11

2-Isopropyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

A solution of 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.150g, 0.521mmol), TEA (0.079g, 0.782mmol) and 4-phenylbutylamine (0.117g, 0.782mmol) in MeCN (3mL) was heated in a microwave reactor at 120°C for 5 mins. The reaction mixture

was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using a 75:25 mixture of heptane and EtOAc as eluant, to give the title compound (0.174 g, 84 %); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.45-7.41 (m, 3H), 7.30-7.26 (m, 2H), 7.22-7.17 (m, 1H), 7.10-7.06 (m, 2H), 5.28-5.23 (m, 1H), 4.45-4.38 (m, 1H), 2.89-2.84 (m, 2H), 2.49-2.44 (m, 2H), 1.59 (d, 6H), 1.43-1.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 141.8, 135.6, 131.8, 129.8, 128.8, 128.6, 128.5, 126.2, 125.3, 106.8, 47.7, 44.2, 35.4, 29.2, 28.3, 20.4; Mass Spectrum: M-H$^+$ 399.

Example 12

2-*tert*-Butyl-4-({3-[3-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

A mixture of 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate (0.120g, 0.244mmol), 3-(hydroxymethyl)phenol (0.030mg, 0.244mmol) and K_2CO_3 (0.168mg, 1.218mmol) in MeCN (2ml) was heated in the microwave reactor at 120°C for 25mins. The reaction mixture was filtered, evaporated and the residue was purified twice by silica gel column chromatography (Horizons Biotage) using 50% EtOAc in hexane and then 0-10%EtOAc in DCM as eluent to give the title compound (0.049mg, 45%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.7.46(m, 2H), 7.45-7.40(m, 3H), 7.30-7.24(m, 1H), 6.96(d, 1H), 6.91(s, 1H), 6.78(d, 1H), 5.73(t, 1H), 4.69(s, 2H), 3.92(t, 2H), 3.11-3.06(m, 2H), 1.88-1.80(m, 2H), 1.74(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 158.8, 142.9, 135.4, 131.8, 129.9, 129.8, 128.8, 125.3, 119.8, 113.9, 112.9, 107.2, 66.0, 65.4, 61.7, 42.4, 28.9, 27.8; Mass Spectrum M+H$^+$ 445.

Example 13

2-*tert*-Butyl-4-{[3-(2-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 2-methoxyphenol and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. Purified by silica gel column chromatography (Horizons Biotage) using 15% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.077mg, 72%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.43-7.40(m, 3H), 6.97-6.94(m, 1H), 6.92-6.88(m, 2H), 6.81(dd, 1H), 5.88(t, 1H), 3.94(t, 2H), 3.89(s, 3H, 3.14-3.09(m, 2H), 1.88-1.84(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ

159.8, 149.9, 148.1, 135.6, 131.8, 129.7, 128.8, 125.5, 121.9, 120.9, 113.8, 111.9, 106.9, 67.5, 61.6, 55.9, 42.6, 29.1, 27.9; Mass Spectrum $M+H^+$ 445.

Example 14

2-*tert*-Butyl-4-({3-[4-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 4-(hydroxymethyl)phenol and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate. Purified by silica gel column chromatography (Horizons Biotage) using 0-10% EtOAc in DCM as eluent to give the title compound (0.037mg, 34%) as a solid. ^1H NMR (500MHz $CDCl_3$): δ 7.54-7.48(m, 2H), 7.46-7.40(m, 3H), 7.29(d, 2H), 6.85(d, 2H), 5.74(t, 1H), 4.64(s, 2H), 3.90(t, 2H), 3.11-3.00(m, 2H), 1.87-1.82(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 158.2, 135.3, 133.8, 131.8, 129.8, 128.9, 128.8, 125.3, 114.7, 107.2, 66.1, 65.2, 61.7, 42.5, 28.9, 27.8, Mass Spectrum $M+H^+$ 445.

Example 15

N-(3-{3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide

A mixture of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.150g, 0.500mmol) and 3-(3-aminopropyloxy)acetanilide (0.208g, 1.000mmol) in MeCN (2ml) was heated in a the microwave reactor at 120°C for 15mins. The mixture was evaporated and the residue purified by silica gel column chromatography (Horizons Biotage) using 50-65% EtOAc in hexane as eluent to give the title compound (0.204mg, 87%). 1H NMR (500MHz $CDCl_3$): δ 7.56-7.50(m, 2H), 7.48-7.42(m, 3H), 7.30-7.24(m, 1H), 7.24-7.18(m, 2H), 6.94(dd, 1H), 6.62(dd, 1H), 5.69(t, 1H), 3.88(t, 2H), 3.12-3.04(m, 2H), 2.18(s, 3H), 1.86-1.80(m, 2H), 1.74(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 168.4, 160.0, 159.4, 139.8, 135.8, 131.8, 129.9, 129.8, 128.8, 125.6, 112.4, 110.9, 106.1, 66.0, 61.8, 42.3, 28.9, 27.8, 25.2; Mass Spectrum $M+H^+$ 472.

Example 16

2-*tert*-Butyl-4-{[3-(2-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 2-fluorophenol and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 15% EtOAc in petroleum ether 40-60°C as eluent then dissolved in EtOAc. The product containing fractions were evaporated and the residue was washed with aqueous K_2CO_3 (2M) and evaporated to give the title compound (0.063g, 62%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.45-7.40(m, 3H), 7.11-7.03(m, 2H), 6.94-6.85(m, 2H), 5.57(t, 1H), 3.91(t, 2H), 3.15-3.10(m, 2H), 1.90-1.82(m, 2H), 1.74(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 153.9, 152.0, 146.8, 146.7, 135.3, 131.8, 129.8, 128.8, 125.2, 124.6, 124.5, 121.9, 121.8, 116.6, 116.5, 115.5, 107.4, 67.2, 61.7, 41.7, 29.2, 27.8. Mass Spectrum M+H$^+$ 433.

Example 17

2-(4-{3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)-N,N-dimethylacetamide

The title compound was prepared as described for Example 12 from 2-(4-hydroxyphenyl)-*N*,*N*-dimethylacetamide and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate. The reaction mixture was evaporated, purified twice by silica gel column chromatography (Horizons Biotage) using 75-85% EtOAc in petroleum ether 40-60°C and then 50% DCM in EtOAc as eluent to give the title compound (0.072g, 59%). 1H NMR (500MHz $CDCl_3$): δ 7.54-7.49(m, 2H), 7.46-7.42(m, 3H), 7.18(d, 2H), 6.82(d, 2H), 5.76(t, 1H), 3.87(t, 2H), 3.66(s, 2H), 3.08(m, 2H), 3.01(s, 3H), 2.98(s, 3H), 1.83(m, 2H), 1.74(s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.5, 159.8, 157.4, 135.3, 131.8, 130.1, 129.7, 128.8, 127.8, 125.3, 114.8, 107.1, 66.1, 61.7, 42.5, 40.3, 37.9, 35.9, 28.9, 27.8; Mass Spectrum M+H$^+$ 500.

Example 18

2-*tert*-Butyl-4-{[3-(2-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 2-chlorophenol and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. The reaction mixture was evaporated and the crude product was purified by silica gel column chromatography (Horizons Biotage)

using 15% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.085g, 77%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.53-7.50(m, 2H), 7.44-7.42(m, 3H), 7.36(dd, 1H), 7.19(dt, 1H), 7.6.92(dt, 1H), 6.83(dd, 1H), 5.56(t, 1H), 3.89(t, 2H), 3.28(m, 2H), 1.88-1.84(m, 2H), 1.74(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 154.2, 135.3, 131.8, 130.6, 129.8, 128.8, 127.9, 125.2, 123.4, 122.1, 113.7, 107.4, 66.7, 61.7, 41.8, 29.2, 27.8; Mass Spectrum $M+H^+$ 449.

Example 19

2-*tert*-Butyl-4-{[3-(3-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 3-methoxyphenol and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. The reaction mixture was evaporated and the crude product was purified by silica gel column chromatography (Horizons Biotage) using 15% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.070g, 65%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.45(m, 2H), 7.45(m, 3H), 7.18(t, 1H), 6.53(dd, 1H), 6.48-6.42(m, 2H), 5.79(t, 1H), 3.89(t, 2H), 3.82(s, 3H), 3.12-3.06(m, 2H), 1.86-1.82(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 161.1, 159.8, 159.7, 135.3, 131.8, 130.2, 129.7, 128.8, 125.3, 107.2, 107.1, 106.6, 101.2, 66.2, 61.7, 55.5, 42.6, 28.9, 27.8; Mass Spectrum $M+H^+$ 445.

Example 20

(3-{3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

A mixture of methyl (3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate (Example 21) (0.087g, 0.179mmol) and LiI (0.239g, 1.788mmol) in pyridine (2ml) was heated at 120°C for 18h. EtOAc was added and the mixture was washed with 1N HCl, evaporated to dryness and the residue was purified by silica gel column chromatography (Horizons Biotage) using 0-12% MeOH (+1% AcOH) in EtOAc as eluent to give the title compound (0.033g, 39%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.46(m, 2H), 7.45-7.40(m, 3H), 7.25(t, 1H), 6.89(dd, 1H), 6.82-6.75(m, 2H), 5.73(t, 1H), 3.87(t, 2H), 3.63(s, 2H), 3.10-3.04(m, 2H), 1.87-1.79(m, 2H), 1.74(s, 9H); ^{13}C NMR

(125MHz $CDCl_3$): δ 176.7, 159.8, 158.7, 135.4, 135.0, 131.8, 129.9, 129.8, 128.8, 125.3, 122.4, 115.7, 113.6, 107.2, 65.9, 61.7, 42.3, 41.2, 29.0, 27.8; Mass Spectrum: $M2H^+$ 472.

Example 21

Methyl (3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

The title compound was prepared as described for Example 12 from methyl (3-hydroxyphenyl)acetate and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 20-40% EtOAc in petroleum ether 40-60°C as eluent. The product containing fractions were evaporated and the residue was dissolved in EtOAc, washed with aqueous K_2CO_3 (2M)and evaporated give the title compound (0.097g, 66%). ^1H NMR (500MHz $CDCl_3$): δ 7.55-7.48(m, 2H), 7.46-7.40(m, 3H), 7.26(t, 1H), 6.90(dd, 1H), 6.82-6.78(m, 2H), 5.76(t, 1H), 3.90(t, 2H), 3.72(s, 3H), 3.61(s, 2H), 3.14-3.06(m, 2H), 1.90-1.80(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 172.1, 159.8, 158.7, 135.7, 135.3, 131.8, 129.9, 129.8, 128.8, 125.3, 122.3, 115.5, 113.4, 107.2, 65.9, 61.7, 52.3, 42.4, 41.4, 29.0, 27.8; Mass Spectrum: $M+H^+$ 487.

Example 22

2-*tert*-Butyl-5-phenyl-4-{[3-(pyridin-4-yloxy)propyl]amino}isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 4-hydroxypyridine and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. EtOAc was added to the reaction mixture and the mixture was washed with water, brine and evaporated. The residue was purified twice by silica gel column chromatography (Horizons Biotage) using 50-80% EtOAc in hexane then 50% EtOAc in DCM as eluent to give the title compound (0.035g, 35%). ^1H NMR (500MHz $CDCl_3$): δ 8.44(d, 2H), 7.54-7.48(m, 2H), 7.48-7.41(m, 3H), 6.75(d, 2H), 5.64(t, 1H), 3.91(t, 2H), 3.114-3.08(m, 2H), 1.90-1.82(m, 2H), 1.74(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 164.5, 159.8, 151.4, 135.2, 131.8, 129.9, 128.9, 125.2, 110.3, 107.6, 65.7, 61.8, 41.9, 28.8, 27.9; Mass Spectrum: $M+H^+$ 416.

Example 23

4-(Benzylamino)-2-*tert*-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

A mixture of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.150g, 0.500mmol) and benzylamine (0.110ml, 1.001mmol) in DMF (2ml) was heated in the microwave reactor at 120°C for 15mins. EtOAc was added, the mixture was washed with brine and evaporated to dryness. The residue was purified by silica gel column chromatography (Horizons Biotage) using 15-20% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.095g, 51%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): δ 7.50-7.38(m, 5H), 7.34-7.25(m, 3H), 7.06-6.98(m, 2H), 5.55(bs, 1H), 4.02(d, 2H), 1.77(9H, s); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 136.8, 133.0, 131.9, 129.8, 129.0, 128.7, 128.2, 127.6, 124.8, 108.2, 61.6, 48.4, 27.9; Mass Spectrum M+H$^+$ 371.

Example 24

2-*tert*-Butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

A mixture of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.150g, 0.500mmol) and (2-phenylethyl)amine (0.121g, 1.001mmol) in MeCN (2ml) was heated in a the microwave reactor at 120°C for 15mins. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 15-20% EtOAc in petroleum ether 40-60°C to give the title compound (0.124g, 65%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.51(m, 2H), 7.51-7.45(m, 3H), 7.30-7.18(m, 3H), 6.87(d, 2H), 5.35(t, 1H), 3.14(q, 2H), 2.62(t, 2H), 1.73(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 137.6, 135.0, 131.8, 129.9, 128.9, 128.7, 127.0, 125.4, 107.5, 61.7, 45.1, 36.0, 27.8; Mass Spectrum M-H$^+$ 384.

Example 25

2-*tert*-Butyl-5-phenyl-4-{[3-(phenylthio)propyl]amino}isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 2-*tert*-butyl-4-[(3-chloropropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and thiophenol at 100°C for 45mins. The reaction mixture was filtered, evaporated to dryness and the residue was purified by silica gel column chromatography (Horizons Biotage) using 10-20% EtOAc in hexane as eluent to give the title compound (0.076g, 65%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.48(m, 2H), 7.46-7.38(m, 3H), 7.32-7.18(m, 5H), 5.32(t, 1H), 3.02-2.96(m, 2H), 2.70(t, 2H), 1.74(s, 9H), 1.68-1.60(m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 135.6, 135.1, 131.8, 129.4,

129.9, 129.3, 128.9, 126.7, 125.1, 107.5, 61.8, 42.8, 31.0, 28.9, 27.9; Mass Spectrum: $M+H^+$ 431.

Example 26

2-*tert*-Butyl-4-[(3-phenoxypropyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 24 from (3-phenoxypropyl)amine and 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide. The residue was purified by silica gel column chromatography (Horizons Biotage) using 17-20% EtOAc in hexane as eluent to give the title compound (0.152g, 73%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.47(m, 2H), 7.44-7.38(m, 3H), 7.32-7.24(m, 2H), 6.95(t, 1H), 6.84(d, 2H), 5.74(t, 1H), 3.87(t, 2H), 3.12-3.04(m, 2H), 1.86-1.78(m, 2H), 1.72(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 158.8, 135.3, 131.8, 129.7, 128.7, 125.3, 121.3, 114.6, 107.2, 65.9, 61.7, 42.5, 29.0, 27.8; Mass Spectrum $M+H^+$ 415.

Example 27

2-*tert*-Butyl-4-{[3-(3-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 3-chlorophenol and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. The reaction mixture was evaporated and purified by silica gel column chromatography (Horizons Biotage) using 15% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.079g, 72%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.46-7.40(m, 3H), 7.20(t, 1H), 6.95(d, 1H), 6.84(s, 1H), 6.75(dd, 1H), 5.67(t, 1H), 3.86(t, 1H), 3.11-3.04(m, 2H), 1.86-1.80(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 159.3, 135.3, 135.1, 131.8, 130.5, 129.8, 128.8, 125.3, 121.5, 115.0, 113.2, 107.4, 66.2, 61.7, 42.4, 28.9, 27.8: Mass Spectrum $M+H^+$ 449.

Example 28

Methyl 3-{3-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoate

The title compound was prepared as described for Example 12 from methyl 3-hydroxybenzoate and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. The reaction

mixture was evaporated and the residue purified by silica gel column chromatography (Horizons Biotage) using DCM as eluent to give the title compound (0.077g, 54%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.66(d, 1H), 7.54-7.48(m, 3H), 4.47-7.42(m, 3H), 7.36(t, 1H), 7.07(dd, 1H), 5.70(t, 1H), 3.94-3.90(m, 5H), 3.13-3.08(m, 2H), 1.90-1.84(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 167.1, 159.8, 158.5, 135.3, 131.8, 131.7, 129.8, 129.7, 128.8, 125.3, 122.6, 120.2, 114.6, 107.3, 66.2, 61.7, 52.4, 42.3, 28.9, 27.8; Mass Spectrum M+H$^+$ 473.

Example 29

2-Benzyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide (Example 1) (0.150g, 0.36 mmol) was dissolved in TFA (3 ml) and heated in a microwave reactor at 120°C for 20 mins. The reaction mixture was concentrated and the residue was repeatedly dissolved in DCM and evaporated. The crude product was dissolved in dry MeCN (3 ml) and potassium carbonate (0.251g, 1.82 mmol) and benzylbromide (0.075g, 0.44 mmol) was added. The reaction mixture was heated at 120°C for 15 mins and then at 130°C for 5 mins in a microwave reactor. The reaction mixture was purified by silica gel column chromatography using a 90:10 mixture of hexane and EtOAc as eluant, to give the title compound (0.088 g, 54 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.49 (m, 4H), 7.48-7.31 (m, 6H), 7.31-7.25 (m, 2H), 7.23-7.17 (m, 1H), 7.11-7.05 (m, 2H), 5.31-5.25 (m, 1H), 4.85 (s, 2H), 2.90-2.82 (m, 2H), 2.50-2.42 (m, 2H), 1.45-1.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 141.7, 135.6, 134.6, 131.8, 130.0, 129.0, 128.9, 128.9, 128.6, 128.5, 128.5, 126.2, 125.1, 107.0, 44.2, 43.8, 35.4, 29.2, 28.3

Mass Spectrum: M-H$^+$ 447.

Example 30

(4-{3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

The title compound was prepared as described for Example 20 from methyl (4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate (Example 32). The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 5% MeOH (+0.5% AcOH) in EtOAc as eluent to give the title compound (0.05g, 8%). ^{1}H NMR (500MHz CD_3OD): δ 7.52-7.44(m,

5H), 7.17(d, 2H), 6.76(d, 2H), 3.78(t, 2H), 3.53(s, 2H), 3.08(t, 2H), 1.79-1.74(m, 2H), 1.17(s, 9H); Mass Spectrum: $M+H^+$ 473.

Example 31

2-*tert*-Butyl-4-{[3-(3-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 12 from 3-fluorophenol and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 15mins. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 15% EtOAc in hexane as eluent to give the title compound (0.069g, 65%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.46-7.42(m, 3H), 7.26-7.20(m, 1H), 6.70-6.60(m, 2H), 6.59-6.55(m, 1H), 5.69(t, 1H), 3.86(t, 1H), 3.12-3.07(q, 2H), 1.90-1.82(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 164.8, 162.8, 159.9, 159.8, 135.3, 131.8, 130.5, 130.4, 129.8, 128.8, 125.3, 110.4, 108.2, 108.1, 107.3, 102.5, 102.3, 66.3, 61.7, 42.3, 28.9, 27.8; Mass Spectrum: $M+H^+$ 433.

Example 32

Methyl (4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

The title compound was prepared as described for Example 12 from methyl (4-hydroxyphenyl)acetate and 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate with a reaction time of 30mins. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 25% EtOAc in hexane as eluent to give the title compound (0.079g, 75%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.44(m, 2H), 7.14-7.38(m, 3H), 7.17(d, 2H), 6.78(d, 2H), 5.72(t, 1H), 3.85(t, 2H), 3.68(s, 3H), 3.56(s, 2H), 3.10-3.00(m, 2H), 1.84-1.78(m, 2H), 1.72(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 172.5, 159.8, 157.7, 135.3, 131.8, 130.7, 130.5, 129.7, 128.8, 126.8, 125.3, 115.7, 114.7, 107.2, 66.1, 61.7, 52.2, 42.4, 40.5, 28.9, 27.8; Mass Spectrum: $M+H^+$ 487.

Example 33

2-*tert*-Butyl-4-{[3-(4-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 5 from 2-*tert*-butyl-4-[(3-bromopropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-fluorophenol using 3 equivalents of K_2CO_3 and with heating at 80°C for 15mins, 100°C for 1h and 120°C for 1h. The reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (Horizons Biotage) using 12-20% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.007g, 31%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.45-7.40(m, 3H), 7.00-6.96(m, 2H), 6.82-6.78(m, 2H), 5.76(t, 1H), 3.86(t, 2H), 3.11-3.02(m, 2H), 1.88-1.80(m, 2H), 1.75(s, 9H); 13C NMR (125MHz $CDCl_3$): δ 159.8, 158., 154.7, 156.7, 135.3, 131.8, 129.7, 128.8, 125.3, 116.2, 160.0, 115.6, 115.5, 107.2, 66.7, 61.7, 42.5, 28.9, 27.8; Mass Spectrum: $M+H^+$ 433.

Example 34

2-Isopropyl-5-phenyl-4-({1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl}amino)isothiazol-3(2H)-one 1,1-dioxide

4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.200g, 0.70mmol), 1-(4-trifluoromethyl-pyrimidin-2-yl)-piperidin-4-ylamine (0.190g, 0.77mmol) and TEA (0.078g, 0.77mmol) was dissolved in dry MeCN (3ml) and heated in a microwave reactor at 120°C for 30 mins. The reaction mixture was purified by silica gel column chromatography using a 65:35 mixture of heptane and EtOAc as eluant, to give the title compound (0.280g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45-8.41 (m, 1H), 7.58-7.52 (m, 2H), 7.49-7.42 (m, 3H), 6.74-6.70 (m, 1H), 5.26-5.19 (m, 1H), 4.59-4.51 (m, 2H), 4.41 (hep, 1H), 3.26-3.16 (m, 1H), 2.58-2.49 (m, 2H), 1.78-1.71 (m, 2H), 1.57 (d, 6H), 1.35-1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 160.3, 158.7, 156.6, 156.3, 134.5, 131.9, 130.2, 129.0, 125.3, 121.8, 119.6, 107.2, 104.9, 50.7, 47.9, 42.4, 32.2, 20.4; Mass Spectrum: $M-H^+$ 496.

Example 35

3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-hydroxybenzoate

The title compound was prepared as described for Example 5 from 2-*tert*-butyl-4-[(3-bromopropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-hydroxybenzoic acid with a reaction time of 1.5h. The reaction mixture was acidified with HCl (1N)and extracted

with EtOAc. The organic layers were combined and evaporated to dryness,. The residue was triturated in MeOH, the solvent was decanted and the residue was purified by silica gel column chromatography (Horizons Biotage) using 50% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.028g, 21%). ^{1}H NMR (500MHz CD_3CN): δ 7.80(d, 2H), 7.62(bs, 1H), 7.56-7.48(m, 2H), 7.56-7.42(m, 3H), 5.93(t, 1H), 4.09(t, 2H), 3.08-3.03(m, 2H), 1.76-1.68(m, 11H); ^{13}C NMR (125MHz CD_3CN): δ 166.5, 160.6, 159.8, 135.2, 132.2, 131.8, 129.9, 128.9, 125.0, 122.2, 115.5, 107.4, 62.2, 61.1, 41.1, 28.4, 27.1; Mass Spectrum: $M+H^+$ 459.

Example 36

4-(Benzylamino)-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.200g, 0.70mmol), benzylamine (0.082g, 0.77mmol) and TEA (0.078g, 0.77mmol) was dissolved in MeCN (3 ml) and heated at in a microwave reactor 120°C for 5 mins. The reaction mixure was purified by silica gel column chromatography using a 75:25 mixture of heptane and EtOAc as eluant, to give the title compound (0.145g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.36 (m, 5H), 7.32-7.26 (m, 3H), 7.05-7.00 (m, 2H), 5.60-5.51 (m, 1H), 4.43 (hep, 1H), 4.08-4.02 (m, 2H), 1.61 (d, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 136.5, 135.2, 131.7, 129.8, 129.0, 128.7, 128.1, 127.5, 124.8, 107.9, 48.3, 47.8, 20.3; Mass Spectrum: $M-H^+$ 357.

Example 37

2-[2-(3-Fluorophenyl)ethyl]-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide (Example 1) (0.150g, 0.36mmol) was dissolved in TFA (3 ml) and heated in a microwave reactor at 120°C for 20 mins. The solvent was evaporated and the crude product was reevaporated from DCM (2x5 ml). The crude product, potassium carbonate (0.251g, 1.82mmol) and 3-fluorophenethylbromide (0.221g, 1.09mmol) was dissolved in dry MeCN (3 ml) and heated at in a microwave reactor 140°C for 10 mins. The reaction mixture was purified by silica gel column chromatography using a 85:15 mixture of heptane and EtOAc as eluant, to give the title compound (0.113g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.41 (m, 5H), 7.34-7.25 (m, 3H), 7.23-7.17 (m, 1H), 7.14-7.01 (m, 4H), 7.00-6.93 (m, 1H), 5.28-5.19 (m, 1H), 3.98-3.90 (m, 2H), 3.18-3.10 (m, 2H), 2.91-2.83 (m, 2H), 2.50-2.43 (m, 2H), 1.44-1.36 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 162.2, 159.1, 141.7, 140.3, 140.2, 135.6, 131.8, 130.4, 130.3, 130.0, 128.9, 128.6, 128.5, 126.2, 125.0, 124.8, 116.2, 116.0, 114.1, 113.9, 107.0, 44.2, 41.1, 35.4, 34.4, 29.2, 28.3; Mass Spectrum: M-H$^+$ 479.

Example 38

4-[(cis-4-Hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was isolated by separation of the mixture of cis and trans isomers of 4-[(4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (50:50, 130mg) by HPLC (C8, 0.05M NH4OAc (pH=4.1):MeCN 1:1) giving the title compound (52mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.48 (m, 2H), 7.45-7.41 (m, 3H), 5.32-5.24 (m, 1H), 4.40 (hep, 1H), 3.78-3.71 (m, 1H), 3.05-2.94 (m, 1H), 1.62-1.40 (m, 6H), 1.58 (d, 6H), 1.32-1.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 134.5, 131.9, 129.9, 128.9, 125.5, 106.3, 65.7, 50.5, 47.8, 31.1, 27.4, 20.4; Mass Spectrum: M-H$^+$ 365.

Example 39

2-*tert*-Butyl-4-[(4-phenoxybutyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Exampel 24 from 1 equivalent of (4-phenoxybutyl)amine, 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1 equivalent TEAat 100°C. The residue was purified by silica gel column chromatography (Horizons Biotage) using 10-20% EtOAc in hexane as eluent giving the title compound (0.172g, 80%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.44-7.38(m, 3H), 7.32-7.25(m, 2H), 6.96(t, 1H), 6.83(d, 2H), 5.34(t, 1H), 3.81(t, 2H), 2.98-2.90(m, 2H), 1.75(s, 9H), 1.64-1.53(m, 4H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 158.9, 135.2, 131.8, 129.8, 129.7, 128.8, 125.3, 121.0, 114.6, 107.2, 67.1, 61.7, 43.9, 27.9, 26.6, 26.4; Mass Spectrum: M+H$^+$ 429.

Example 40

2-*tert*-Butyl-4-({3-[(1-oxidopyridin-3-yl)oxy]propyl}amino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-5-phenyl-4-{[3-(pyridin-3-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide (Example 5) (0.202g, 0.49mmol) was dissolved in dry DCM (15 ml) and cooled to 0°C with an icebath. *m*CPBA (70%) (0.120g, 0.53mmol) was added and the icebath was removed and

the reaction mixture was allowed to reach rt. After stirring for 2h the reaction mixture was extracted with saturated aqueous $NaHCO_3$ solution (20 ml) and brine (20 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography using a 10:90 mixture of heptane and EtOAc and then DCM:MeOH 97:3 as eluant, to give the title compound (0.160g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90-7.83 (m, 2H), 7.51-7.37 (m, 5H), 7.16-7.09 (m, 1H), 6.80-6.74 (m, 1H), 5.68-5.57 (m, 1H), 3.85-3.76 (m, 2H), 3.09-3.02 (m, 2H), 1.85-1.76 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 157.0, 135.1, 133.0, 131.8, 129.9, 128.9, 128.2, 125.7, 125.2, 113.5, 107.6, 67.0, 61.8, 60.6, 41.7, 32.1, 28.8, 27.8, 22.9; Mass Spectrum: M-H$^+$ 432.

Example 41

2-*tert*-Butyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 24 from (2-phenoxyethyl)amine and 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide. The residue was purified by silica gel column chromatography (Horizons Biotage) using 15-20% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.026g, 13%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.60-7.51(m, 2H), 4.72-7.42(m, 2H), 7.29(t, 2H), 6.99(t, 1H), 6.84(d, 2H), 5.67(t, 1H), 3.89(t, 2H), 3.25(q, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.7, 158.3, 135.2, 131.7, 129.5, 129.8, 129.0, 125.2, 121.7, 114.7, 108.1, 65.9, 61.8, 43.5, 27.8.; Mass Spectrum M+H$^+$ 401.

Example 42

4-(Benzylamino)-2-cyclopentyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-(benzylamino)-2-*tert*-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide (Example 23) and bromocyclopentane in a similar way as described for Example 2 and 3. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.48-7.36 (m, 5H), 7.31-7.26 (m, 3H), 7.04-6.99 (m, 2H), 5.61-5.53 (m, 1H), 4.39 (p, 1H), 4.05 (d, 2H), 2.27-2.10 (m, 4H), 1.97-1.87 (m, 2H), 1.7-1.6 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$):δ 158.8, 136.5, 135.2, 131.7, 129.8, 128.9, 128.7, 128.1, 127.4, 124.9, 107.9, 55.2, 48.3, 29.4, 24.1; Mass Spectrum: M-H$^+$ 383.

Example 43

2-*tert*-Butyl-4-{[3-(4-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-[(3-bromopropyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-methoxyphenol in a similar manner as described for e.g Example 5 and 33 and 35. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.46-7.42(m, 3H), 6.86-6.78(m, 4H), 5.79(t, 1H), 3.85(t, 2H), 3.79(s, 3H), 3.12-3.04(m, 2H), 1.85-1.80(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 154.3, 152.7, 135.4, 131.8, 129.7, 128.8, 125.4, 115.5, 114.9, 107.1, 66.8, 61.7, 55.9, 42.6, 29.1, 27.9.; Mass Spectrum: M+H$^+$ 445.

Example 44

4-[(4,4-Difluorocyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.155g, 0.54mmol), 4,4-difluorocyclohexylamine (0.11g, 0.81mmol) and TEA (0.082g, 0.81mmol) was dissolved in dry MeCN (3 ml) and heated in a microwave reactor at 130°C for 10 mins. The reaction mixture was purified by silica gel column chromatography using a 85:15 mixture of hexane and EtOAc as eluant, to give the title compound (0.142g, 68%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.49-7.42 (m, 3H), 5.23-5.16 (m, 1H), 4.41 (hep, 1H), 3.10-3.00 (m, 1H), 1.97-1.86 (m, 2H), 1.77-1.68 (m, 2H), 1.57 (d, 6H), 1.49-1.37 (m, 2H), 1.37-1.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 134.5, 131.8, 130.3, 129.0, 125.1, 123.9, 122.0, 120.0, 107.3, 49.9, 47.9, 32.1, 31.9, 31.7, 29.0, 28.9, 20.4; Mass Spectrum: M-H$^+$ 385.

Example 45

4-(Benzylamino)-2-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and benzylamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (CD_3CN) δ 7.47-7.42 (m, 1H), 7.40-7.35 (m, 2H), 7.34-7.29 (m, 2H), 7.23-7.18 (m, 3H), 6.88-6.83 (m, 2H), 6.44-6.35 (m, 1H), 4.16 (d, *J*=6.6Hz, 2H), 3.68 (t, *J*=7.3Hz, 2H), 1.82-1.71 (m, 2H), 1.49-1.38 (m, 2H), 0.98 (t, *J*=7.4Hz, 3H); Masspectrum: M+H$^+$ 371.

Example 46

2-Butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 2-phenylethanamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.52(m, 2H), 7.50-7.42(m, 2H), 7.30-7.20(m, 4H),

6.88(dd, 2H), 5.38(t, 1H), 3.70(t, 2H), 3.18(dt, 2H), 2.62(t, 2H), 1.88-1.78(m, 2H), 1.50-1.40(m, 2H), 0.98(t, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.4, 137.8, 137.5, 131.8, 130.0, 129.0, 128.9, 128.7, 127.1, 125.2, 107.2, 45.1, 40.4, 36.0, 30.4, 20.3, 13.8; Mass -Spectrum $M+H^+$ 385.

Example 47

2-Butyl-4-{[4-(difluoromethoxy)benzyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-[4-(difluoromethoxy)phenyl]methanamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (CD_3CN) δ 7.46-7.41 (m, 1H), 7.39-7.33 (m, 2H), 7.29-7.25 (m, 2H), 6.98-6.93 (m, 2H), 6.86-6.81 (m, 2H), 6.72 (t, *J*=74.4Hz, 1H), 6.48-6.39 (m, 1H), 4.16 (d, *J*=6.6Hz, 2H), 3.67 (t, *J*=7.2Hz, 2H), 1.81-1.72 (m, 2H), 1.49-1.38 (m, 2H), 0.98 (t, *J*=7.3Hz, 3H); Masspectrum: $M+H^+$ 437.

Example 48

4-[(trans-4-Hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was isolated by separation of a mixture of the cis and trans isomers of 4-[(4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (50:50, 130mg) by HPLC (C8, 0.05M NH4OAc (pH=4.1):MeCN 1:1) giving the title compound (73mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.46-7.42 (m, 3H), 5.16-5.08 (m, 1H), 4.39 (hep, 1H), 3.52-3.42 (m 1H), 2.96-2.85 (m, 1H), 1.82-1.70 (m, 4H), 1.57 (d, 6H), 1.16-1.06 (m, 2H), 0.88-0.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 134.7, 131.8, 130.1, 128.9, 125.2, 106.5, 69.4, 51.3, 47.8, 33.5, 31.0, 20.4; Mass Spectrum: $M-H^+$ 365.

Example 49

2-*tert*-Butyl-4-[(3-hydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

A mixture of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.300g, 1.001mmol), 3-hydroxypropyamine (0.08ml, 1.001mmol) and TEA (0.14ml, 1.001mmol) in MeCN (5ml) was stirred at rt. After 18h the mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (Horizons Biotage) eluting with 33-80% EtOAc (+0.5% TEA) in petroleum ether 40-60°C to give the title compound (0.145g,

43%). 1H NMR (500MHz, $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.46-7.42 (m, 3H), 5.77 (t, 1H), 3.62 (q, 2H), 3.01 (q, 2H), 1.74 (s, 9H), 1.63 (qt, 2H); Mass Spectrum: M-H^+ 337.

Example 50

5-Phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-3-ylmethyl)isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-*tert*-butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide (Example 1) and 3-(bromomethyl)pyridine in a similar manner as described for e.g. Example 2 and 3 ^1H NMR (500 MHz, $CDCl_3$):δ 8.80-8.76 (m, 1H), 8.62-8.58 (m, 1H), 7.89-7.85 (m, 1H), 7.53-7.41 (m, 5H), 7.34-7.24 (m, 3H), 7.22-7.17 (m, 1H), 7.09-7.04 (m, 2H), 5.31-5.25 (m, 1H), 4.84 (s, 2H), 2.90-2.83 (m, 2H), 2.49-2.42 (m, 2H), 1.44-1.35 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.1, 150.3, 149.8, 141.6, 136.7, 135.5, 131.7, 130.3, 130.0, 128.8, 128.5, 128.4, 126.1, 124.7, 123.7, 107.0, 44.1, 41.1, 35.3, 29.0, 28.2; Mass Spectrum: M-H^+ 448.

Example 51

2-Butyl-4-[(4-hydroxycyclohexyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-aminocyclohexanol in a similar manner as described for e.g. Example 6 and 7 affording a mixture of cis and trans isomeres. ^1H NMR (500MHz, CD_3CN): δ 0.61-0.72 (m, 2H), 0.95-0.99 (m, 6H), 1.02-1.10 (m, 2H), 1.17-1.27 (m, 2H), 1.38-1.60 (m, 12H), 1.64-1.80 (m, 8H), 2.46 (d, 1H), 2.55 (d, 1H), 2.86-3.05 (m, 2H), 3.29-3.38 (m, 1H), 3.60-3.69 (m, 5H), 5.55-5.66 (m, 2H), 7.47-7.57 (m, 10H).

Example 52

4-{3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

Methyl 4-{3-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoate (0.90g, 0.19mmol) and LiI (0.382g, 2.86mmol) was dissolved in dry pyridine (1mL) and heated at reflux for 4h and then left at rt over night. The reaction mixture was purified by flash chromatography using first Hexane and EtOAc and then EtOAc and MeOH as eluant giving the title compound (0.003g, 3.4%). ^1H NMR(CD3CN): 7.98(d, 2H),

7.56-7.48(m, 5H), 6.90(d, 2H), 6.02(t, 1H), 3.90(t, 2H), 3.12-3.08(m, 2H), 1.82-1.76(t, 2H), 1.17(s, 9H); Mass Spectrum:M+H$^+$ 459.

Example 53

2-*tert*-Butyl-4-{[3-(4-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-[(3-bromopropyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-chlorophenol in a similar manner as described for Example 5. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.48(m, 2H), 7.46-7.40(m, 3H), 7.26-7.20(m, 2H), 6.82-6.76(m, 2H), 5.72(t, 1H), 3.86(t, 2H), 3.11-3.06(m, 2H), 1.88-1.80(m, 2H), 1.75(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 157.1, 135.3, 131.8, 129.8, 129.6, 128.8, 126.2, 125.3, 115.9, 107.3, 66.4, 61.7, 42.4, 28.9, 27.8.; Mass Spectrum: M+H$^+$ 449.

Example 54

5-Phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-4-ylmethyl)isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-*tert*-butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide (Example 1) and 4-(chloromethyl)pyridine in a similar manner as described for e.g. Example 2 and 3 ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.66-8.60 (m, 2H), 7.54-7.38 (m, 7H), 7.31-7.24 (m, 2H), 7.23-7.16 (m, 1H), 7.10-7.04 (m, 2H), 5.34-5.27 (m, 1H), 4.82 (s, 2H), 2.92-2.84 (m, 2H), 2.50-2.42 (m, 2H), 1.45-1.35 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.3, 150.3, 143.4, 141.5, 135.4, 131.7, 130.0, 128.8, 128.5, 128.4, 126.1, 124.7, 123.1, 107.2, 44.1, 42.3, 35.3, 31.5, 29.0, 28.2; Mass Spectrum: M-H$^+$ 448.

Example 55

4-[(1,3-Benzodioxol-5-ylmethyl)amino]-2-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-(1,3-benzodioxol-5-yl)methanamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (500MHz, CD_3CN): δ 0.97 (t, 3H), 1.39-1.48 (m, 2H), 1.72-1.80 (m, 2H), 3.67 (t, 2H), 4.05 (d, 2H), 5.91 (s, 2H), 6.26-6.34 (m, 2H), 6.64 (d, 1H), 7.32-7.48 (m, 5H).

Example 56

4-(2,3-Dihydro-1H-inden-2-ylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and indan-2-aminein a similar manner as desribed for Example 1. ^{1}H NMR (400 MHz, CD_3CN): δ 7.65-7.60 (m, 2H), 7.55-7.50 (m, 3H), 7.13-7.11 (m, 4H), 5.90 (d, 1H), 4.06-3.98 (m, 1H), 3.83 (t, 2H), 3.67 (t, 2H), 3.38 (s, 3H), 2.84-2.81 (m, 4H); Mass Spectrum: M+H$^+$ 399.

Example 57

2-Butyl-4-[(2-morpholin-4-ylethyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 2-morpholin-4-ylethanamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.50(m, 2H), 7.50-7.00(m, 3H), 6.05(t, 1H), 3.78-3.65(m, 6H), 2.92-2.88(m, 2H), 2.46-2.32(m, 6H), 1.88-1.80(m, 2H), 1.50-1.42(m, 2H), 1.00(t, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.2, 135.9, 131.6, 129.8, 128.9, 125.3, 107.2, 67.1, 56.4, 53.2, 40.3, 40.2, 30.5, 20.3, 13.8.; Mass Spectrum: M+H$^+$ 394.

Example 58

2-*tert*-Butyl-4-{[3-(4-isopropylphenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate and 4-isopropylphenol in a similar manner as described for Example 12. ^{1}H NMR (500MHz $CDCl_3$): δ 7.56-7.50(m, 2H), 7.48-7.42(m, 3H), 7.16(d, 2H), 6.80(d, 2H), 5.78(t, 1H), 3.88(t, 2H), 3.10-3.05(m, 2H), 2.92-2.82(m, 1H), 1.85-1.80(m, 2H), 1.75(s, 9H), 1.24(d, 6H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 156.6, 141.8, 135.4, 131.8, 129.7, 128.8, 127.5, 125.4, 114.4, 107.1, 66.1, 61.7, 42.6, 33.5, 29.0, 27.9, 24.4; Mass Spectrum: M+H$^+$ 457.

Example 59

4-({3-[Benzyl(butyl)amino]propyl}amino)-2-tert-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-[(3-bromopropyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and N-benzylbutan-1-amine in a similar manner as described for Example 5. ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.44(m, 2H), 7.42-7.38(m, 3H), 7.33-7.30(m, 2H), 7.30-7.24(m, 3H), 6.36(t, 1H), 3.48(s, 2H), 2.86-2.78(m, 2H), 2.40-2.12(m, 4H), 1.76(s, 9H), 1.56-1.44(m, 4H), 1.36-1.24(m, 2H), 0.91(t, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 139.4, 135.6, 131.8, 129.4, 129.2, 128.9, 128.4, 127.2, 125.7, 106.3, 61.5, 59.2, 54.1, 52.0, 44.3, 29.2, 27.8, 26.3, 20.9, 14.3; Mass Spectrum: M+H$^+$ 484.

Example 60

2-*tert*-Butyl-4-{[3-(3,5-dipropoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-[(3-bromopropyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 3,5-dipropoxyphenol in a similar manner as described for Example 5. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.46-7.41 (m, 3H), 6.12-6.09 (m, 1H), 6.08-6.06 (m, 2H), 5.89-5.83 (m, 1H), 3.93-3.84 (m, 6H), 3.09-3.03 (m, 2H), 1.87-1.76 (m, 6H), 1.74 (s, 9H), 1.07-1.01 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 160.2, 159.9, 135.4, 131.8, 129.7, 128.8, 125.3, 107.1, 94.8, 94.6, 94.4, 94.0, 69.8, 66.4, 61.6, 42.7, 28.8, 27.8, 22.8, 10.8; Mass Spectrum: M+H$^+$ 531.

Example 61

2-*tert*-Butyl-4-[(2,2-diphenylethyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 2,2-diphenylethanamine in a similar manner as described for Example 1. ^{1}H NMR (500MHz $CDCl_3$): δ 7.59-7.54(m, 2H), 7.48-7.43(m, 3H), 7.27(t, 4H), 7.22(t, 2H), 6.97(d, 4H), 5.25(t, 1H), 3.96(t, 1H), 3.50(dd, 2H), 1.70(s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.6, 140.8, 135.0, 131.7, 129.9, 129.0, 128.0, 127.3, 125.3, 108.1, 61.7, 50.7, 48.3, 27.8; Mass Spectrum: M+H$^+$ 461.

Example 62

2-Ethyl-4-{[2-(1H-imidazol-4-yl)ethyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-ethyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 2-(1H-imidazol-4-yl)ethanamine in a similar manner as described for Exmple 1. ^{1}H NMR (500 MHz, CD_3OD): δ 7.54-7.42 (m, 6H), 6.51-6.48 (m, 1H), 3.71 (q, 2H), 3.14 (t,

2H), 2.55 (t, 2H), 1.36 (t, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 159.9, 137.3, 136.1, 132.9, 132.3, 130.6, 129.7, 126.9, 117.2, 107.2, 44.6, 36.0, 27.8, 14.0; Mass Spectrum: M+H$^+$ 347.

Example 63

2-Butyl-4-[(4-morpholin-4-ylbenzyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-(4-morpholin-4-ylphenyl)methanamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.48(m, 2H), 7.46-7.40(m, 3H), 6.94(d, 2H), 6.81(d, 2H), 5.47(t, 1H), 3.95(d, 2H), 3.87(t, 4H), 3.72(t, 2H), 3.15(t, 4H), 1.88-1.80(m, 2H), 1.52-1.42(m, 2H), 0.99(t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 151.3, 135.8, 131.8, 129.9, 128.9, 128.8, 127.6, 125.1, 115.9, 108.0, 67.0, 49.4, 48.1, 40.4, 30.5, 20.3, 13.8; Mass Spectrum: M+H$^+$ 456.

Example 64

2-Butyl-4-{[3-(2-methoxyethoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide 3-(2-methoxyethoxy)propan-1-amine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.50(m, 2H), 7.48-7.42(m, 3H), 6.04(t, 1H), 3.70(t, 2H), 3.58(s, 4H), 3.46(t, 2H), 3.40(s, 3H), 3.04-2.98(m, 2H), 1.88-1.80(m, 2H), 1.70-1.66(m, 2H), 1.50-1.40(m, 2H), 0.98(t, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.2, 135.9, 131.8, 129.7, 128.8, 125.4, 106.4, 72.1, 70.7, 69.9, 59.3, 43.3, 40.2, 30.5, 28.9, 20.3, 13.8; Mass Spectrum: M+H$^+$ 397.

Example 65

2-Butyl-4-[(3-morpholin-4-ylpropyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 3-morpholin-4-ylpropan-1-amine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58(bs, 1H), 7.58-7.52(m, 2H), 7.48-7.40(m, 3H), 3.84-3.78(m, 4H), 3.70(t, 2H), 2.98-2.92(m, 2H), 2.50-2.38(m, 6H), 1.86-1.80(m, 2H), 1.62-1.52(m, 2H), 1.50-1.40(m, 2H), 0.98(t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 136.4, 131.8, 129.5, 128.7, 125.7, 105.9, 66.9, 58.3, 54.0, 45.6, 40.2, 30.5, 24.1, 20.3, 13.8; Mass Spectrum: M+H$^+$ 408.

Example 66

2-Butyl-4-[(2-methoxyethyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 2-methoxyethanamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (400 MHz, CD_3CN): δ 7.55-7.49 (m, 5H), 5.83 (bs, 1H), 3.67 (t, 2H), 3.27 (t, 2H), 3.21 (s, 3H), 3.05-3.00 (m, 2H), 1.80-1.72 (m, 2H), 1.48-1.38 (m, 2H), 0.97 (t, 3H); Mass Spectrum: $M+H^+$ 339.

Example 67

2-(2-Methoxyethyl)-5-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and tetrahydro-2H-pyran-4-amine in a similar manner as desribed for Example 1. ^{1}H NMR (400 MHz, CD_3CN): δ 7.58-7.50 (m, 5H), 5.70 (d, 1H), 3.84 (t, 2H), 3.74-3.66 (m, 4H), 3.35 (s, 3H), 3.21-3.10 (m, 1H), 2.86-2.78 (m, 2H), 1.61-1.54 (m, 2H), 1.48-1.36 (m, 2H); Mass Spectrum: $M+H^+$ 367.

Example 68

4-(Hexylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and hexan-1-amine in a similar manner as desribed for Example 1. ^{1}H NMR (400 MHz, CD_3CN): δ 7.48-7.56 (m, 5H), 5.83-5.99 (m, 1H), 3.83 (t, 2H), 3.67 (t, 2H), 3.35 (s, 3H), 2.84-2.90 (m, 2H), 1.13-1.32 (m, 4H), 0.92-1.09 (m, 4H), 0.82 (t, 3H); Mass Spectrum: $M-H^+$ 365.

Example 69

4-[(4-Hydroxycyclohexyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-aminocyclohesanol in a similar manner as desribed for Example 1. ^{1}H-NMR(CD_3CN): δ 7.58-7.48 (m, 5H), 5.66 (d, J =8.5Hz, 1H), 3.83 (t, J =5.7Hz, 2H), 3.67 (t, J =5.7Hz, 2H), 3.65-3.60 (m, 1H), 3.35 (s, 3H), 3.06-2.95 (m, 1H), 2.49 (d, J = 3.5Hz, 1H), 1.62-1.35 (m, 6H), 1.11-0.99 (m, 2H);MS (ESI+) 381.06 ($M + 1H^+$).

Example 70

4-[(1,3-Benzodioxol-5-ylmethyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-(1,3-benzodioxol-5-yl)methanamine in a similar manner as desribed for Example 1. ^{1}H NMR (400 MHz, CD_3CN): δ 7.32-7.49 (m, 5H), 6.64 (d, 1H), 6.31-6.38 (m, 2H), 6.25-6.29 (m, 1H), 5.91 (s, 2H), 4.05 (d, 2H), 3.83 (t, 2H), 3.67 (t, 2H), 3.35 (s, 3H); Mass Spectrum: M-H$^+$ 415.

Example 71

2-Butyl-4-[(4-methoxybenzyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-(4-methoxyphenyl)methanamine in a similar manner as described for e.g. Example 6 and 7. ^{1}H NMR (CD_3CN) δ 7.50-7.33 (m, 5H), 6.79-6.74 (m, 4H), 6.34-6.26 (m, 1H), 4.08 (d, *J*=6.7Hz, 2H), 3.75 (s, 3H), 3.67 (t, *J*=7.2Hz, 2H), 1.81-1.71 (m, 2H), 1.49-1.38 (m, 2H), 0.97 (t, *J*=7.5 Hz, 3H); Masspectrum: M-H$^+$ 399.

Example 72

5-Phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-2-ylmethyl)isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-*tert*-butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide (Example 1) and 2-(bromomethyl)pyridine in a similar manner as described for e.g. Example 2 and 3. ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.65-8.60 (m, 1H), 7.74-7.67 (m, 1H), 7.56-7.51 (m, 2H), 7.50-7.41 (m, 4H), 7.31-7.17 (m, 4H), 7.10-7.05 (m, 2H), 5.35-5.28 (m, 1H), 5.01 (s, 2H), 2.94-2.84 (m, 2H), 2.50-2.42 (m, 2H), 1.45-1.35 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.4, 154.4, 149.7, 141.6, 137.1, 135.5, 131.7, 129.9, 128.8, 128.5, 128.4, 126.1, 124.9, 123.0, 121.9, 107.2, 44.9, 44.1, 35.3, 29.1, 28.2; Mass Spectrum: M-H$^+$ 448.

Example 73

2-*tert*-Butyl-4-{[3-(3-hydroxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

A mixture of 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate (0.045g, 0.091mmol), resorcinol (0.020g, 0.183mmol) and K_2CO_3 (0.063g, 0.457mmol) in MeCN (2ml) was heated in a microwave reactor at 120°C for 10mins. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 0-50% EtOAc in DCM as eluent to give the title compound (0.016g, 41%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.48 (m, 2H), 7.46-7.41 (m, 3H), 7.13 (t, 1H), 6.46-6.41 (m, 2H), 6.39-6.36 (m, 1H), 5.75 (t, 1H), 5.14 (s, 1H), 3.86 (t, 2H), 3.11-3.04 (m, 2H), 1.86-1.78 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): 159.9, 157.1, 135.4, 131.8, 130.4, 129.8, 128.8, 125.3, 108.5, 107.1, 106.9, 102.3, 66.1, 61.8, 42.5, 28.9, 27.8; Mass Spectrum: M+H$^+$ 431.

Example 74

3-{3-[(2-tert-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

The title compound was prepared from 3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-methylbenzenesulfonate and 3-hydroxybenzoic acid in a similar manner as described for Example 12.

^{1}H NMR (500 MHz, *d8*-THF): δ 7.62-7.58 (d, 1H), 7.57-7.51 (m, 2H), 7.49 (s, 1H), 7.46-7.42 (m, 3H), 7.31 (t, 1H), 7.30 (t, 1H), 6.51 (t, 1H), 3.82 (t, 2H), 3.14-3.08 (m, 2H), 1.83-1.78 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, *d8*-THF): δ 166.7, 159.8, 158.9, 135.5, 132.5, 131.9, 129.2, 129.1, 128.4, 126.4, 122.1, 119.1, 114.9, 106.9, 65.6, 60.4, 41.3, 29.0, 26.9; Mass Spectrum: M+H$^+$ 459.

Example 75

2-*tert*-Butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide

TFA (1ml) was added to a solution of *tert*-butyl 4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidine-1-carboxylate (Example 86) (2.138g, 4.612mmol) in DCM (20ml) and the mixture was stirred at rt for 80mins. TFA (1ml) was added and the reaction mixture was stirred for 18h. The reaction mixture was basified by addition of saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, and evaporated to give the title compound (1.630g, 97%) as a solid. 1H NMR (500MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.40 (m, 3H), 5.20 (d, 1H), 3.08-2.92 (m, 3H), 2.19 (dt, 2H), 1.74

(s, 9H), 1.72-1.46 (m, 2H), 1.36-1.24 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.9, 134.0, 131.8, 130.1, 128.9, 125.3, 107.1, 61.8, 50.2, 44.7, 33.1, 27.9; Mass Spectrum: $M+H^+$ 364.

Example 76

2-*tert*-Butyl-4-[(2-hydroxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

The title compound was prepared as described for Example 49 from 2-aminoethanol and 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide. The residue was purified by silica gel column chromatography (Horizons Biotage) using DCM as eluent to give the title compound (1.788g, 55%) as an oil. 1H NMR (500MHz,): δ 7.50-7.44 (m, 5H), 6.81 (t, 1H), 4.69 (t, 1H), 3.29-3.22 (m, 2H), 3.86-2.80 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (125MHz DMSO-d_6): 159.9, 136.1, 132.1, 130.0, 129.2, 125.9, 105.4, 61.2, 59.5, 46.6, 27.8; Mass Spectrum: $M+H^+$ 325.

Example 77

4-{2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol) 4-(2-aminoethyl)phenyl methanesulfonate (0.149g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.140g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H), 7.48-7.43 (m, 3H), 7.14-7.10 (m, 2H), 6.83-6.78 (m, 2H), 5.43-5.36 (m, 1H), 3.15-3.08 (m, 2H), 2.61-2.55 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 148.2, 137.1, 134.9, 131.9, 130.3, 130.0, 129.0, 125.3, 122.4, 107.7, 61.8, 44.9, 37.6, 35.5, 27.8; Mass Spectrum: $M-H^+$ 479.

Example 78

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzenesulfonamide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), 4-(2-aminoethyl)benzenesulfonamide (0.139g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.122g, 45%). ^{1}H NMR (500 MHz, *d8*-THF): δ 7.70-7.65 (m, 2H), 7.58-7.52 (m, 2H), 7.51-7.45 (m,

3H), 6.90-6.84 (m, 2H), 6.53-6.47 (m, 1H), 6.38-6.34 (m, 1H), 3.19-3.12 (m, 2H), 2.64-2.58 (m, 1H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, *d8*-THF): δ 159.7, 143.3, 142.4, 135.2, 132.0, 129.4, 128.8, 128.6, 126.4, 126.3, 107.2, 60.6, 44.7, 35.6, 27.0; Mass Spectrum: M-H$^+$ 464.

Example 79

2-*tert*-Butyl-4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (200mg, 0.667mmol) was dissolved in dry DMF (2mL) under nitrogen atmosphere. 1-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-amine (188mg, 0.674mmol) was added followed by TEA (68mg, 0.667mmol) and the reaction mixture was heated in a microwave reactor at 120°C for 20 mins.. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$-solution, dried over Na_2SO_4, filtered and evaporated. The crude product was purified on a Biotage Horizon HPFC system using Heptane and EtOAc as eluant affording the title compound (284mg, 77.6%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46-1.54 (m, 2H), 1.73-1.79 (m, 11H), 2.51 (t, 2H), 3.12-3.19 (m, 1H), 3.79-3.82 (m, 2H), 5.28 (d, 1H), 7.44-7.46 (m, 3H), 7.53-7.55 (m, 2H), 7.72 (s, 1H), 8.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.82, 32.36, 47.43, 50.27, 61.80, 107.32, 120.35 (q, J=33.4Hz), 121.28, 123.48 (q, J=271.3Hz), 125.36, 128.94, 130.17, 131.85, 134.16, 136.15, 143.10, 159.87, 160.06; Mass Spectrum: M+H$^+$ 543.1.

Example 80

tert-Butyl 3-{2-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}azetidine-1-carboxylate

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (74mg, 0.249mmol) was dissolved in dry DMF (1mL) nitrogen atmosphere. *tert*-Butyl 3-(2-aminoethyl)azetidine-1-carboxylate (50mg, 0.249mmol) was added followed by TEA (25mg, 0.247mmol) and the reaction mixture was heated in a microwave reactor for at 120°C for 20 mins. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$-solution, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by preparative HPLC affording the title compound (33mg, 28.8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.62 (q, 2H), 1.73 (s, 9H), 2.19-2.27 (m, 1H), 2.83 (q, 2H), 3.23-3.26 (m, 2H), 3.84 (t, 2H), 5.25 (t, 1H), 7.42-7.51 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.24, 27.82, 28.61, 34.35,

41.72, 54.06, 61.82, 79.63, 107.55, 125.15, 128.93, 130.09, 131.79, 135.04, 156.38, 159.81; Mass Spectrum: M-H$^+$ 462.

Example 81

4-{2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), 4-(2-aminoethyl)benzonitrile (0.101g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.039g, 16%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.43 (m, 7H), 6.88-6.84 (m, 2H), 5.39-5.33 (m, 1H), 3.17-3.10 (m, 2H), 2.65-2.60 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 143.2, 134.7, 132.7, 131.8, 130.1, 129.5, 129.1, 125.2, 118.8, 111.1, 108.1, 61.9, 44.5, 41.2, 36.2, 27.8; Mass Spectrum: M-H$^+$ 410.

Example 82

2-*tert*-Butyl-4-(isopropylamino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), isopropylamine (0.041g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.108g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.46 (m, 2H), 7.44-7.38 (m, 3H), 5.16-5.04 (m, 1H), 3.34-3.22 (m, 1H), 1.71 (s, 9H), 0.94 (d, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 134.2, 131.7, 129.8, 128.9, 125.6, 106.5, 61.6, 44.8, 27.8, 23.0; Mass Spectrum: M-H$^+$ 323.

Example 83

2-*tert*-Butyl-5-phenyl-4-{[3-(pyridin-2-yloxy)propyl]amino}isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 24 from 1 equivalent of [3-(pyridin-2-yloxy)propyl]amine, 2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1 equivalent TEA with a reaction time of 30mins. The residue was purified by silica gel column chromatography (Horizons Biotage) using 5:1 petroleum ether 40-60°C in EtOAc as eluent to give the title compound (0.178g, 65%) as a solid. ^{1}H NMR (500MHz

$CDCl_3$): δ 8.17 (dd, 1H), 7.62-7.57 (m, 1H), 7.54-7.48 (m, 2H), 7.45-7.40 (m, 3H), 6.91-6.88 (m, 1H), 6.74 (d, 1H), 6.00 (t, 1H), 4.28 (t, 2H), 3.04 (q, 2H), 1.83 (quintet, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 163.8, 159.9, 147.0, 138.9, 135.5, 131.8, 129.7, 128.8, 125.4, 117.3, 111.5, 106.9, 63.6, 61.6, 42.0, 28.9, 27.9; Mass Spectrum: $M+H^+$ 416.

Example 84

2-*tert*-Butyl-4-{[1-(5-methylpyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (97mg, 0.324mmol) was dissolved in dry DMF (1mL) under nitrogen atmosphere. 1-(5-Methylpyridin-2-yl)piperidin-4-amine dihydrochloride (86mg, 0.327mmol) was added followed by TEA (33g, 0.324mmol). The reaction mixture was heated in a microwave reactor for at 120°C for 25mins. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$-solution and water. The organic phase was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by preparative HPLC affording the title compound (64mg, 43.5%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.33-1.41 (m, 2H), 1.71-1.74 (m, 11H), 2.17 (s, 3H), 2.38-2.43 (m, 2H), 3.08- 3.15 (m, 1H), 3.95-3.99 (m, 2H), 5.23 (d, 1H), 6.51 (d, 1H), 7.26 (dd, 1H), 7.43-7.45 (m, 3H), 7.53-7.55 (m, 2H), 7.96 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.51, 27.84, 32.05, 44.64, 50.68, 61.78, 107.10, 107.50, 122.63, 125.39, 128.91, 130.11, 131.90, 134.20, 138.65, 147.86, 157.77, 159.91; Mass Spectrum: $M+H^+$ 455.0.

Example 85

2-*tert*-Butyl-4-{[1-(6-chloropyridazin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.450g, 1.50mmol), 1-(6-chloropyridazin-3-yl)piperidin-4-amine (0.487g, 1.95mmol) and TEA (0.456g, 4.50mmol) was dissolved in dry MeCN (15 ml) and heated in a microwave reactor at 120°C for 30 mins. The reaction mixture was evaporated and the residue was diluted with EtOAc (150 ml) and washed with water (500 ml). The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography using a 60:40→50:50 mixture of heptane and EtOAc as eluant, to give the title compound (0.191g, 27%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.47-7.43 (m, 3H), 7.15 (d, 1H), 6.81 (d, 1H), 5.20 (d, 1H), 4.11-4.05 (m, 2H), 3.22-3.13 (m, 1H), 2.60-2.52 (m, 2H), 1.80-

1.73 (m, 2H), 1.72 (s, 9H), 1.41-1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 158.6, 147, 133.8, 131.6, 130, 128.8, 128.7, 125, 115.4, 107.3, 61.6, 50, 43.8, 31.6, 27.6.

Example 86

***tert*-Butyl 4-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidine-1-carboxylate**

A mixture of 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (2.000g, 6.672mmol), *tert*-butyl 4-aminopiperidine-1-carboxylate (1.336g, 6.672mmol) and TEA (0.933ml, 6.672mmol) in MeCN (20ml) was heated in a microwave reactor at 120°C for 40mins and 130°C for 30mins. *tert*-Butyl 4-aminopiperidine-1-carboxylate (0.267mg, 1.334mmol) and TEA (0.187ml, 1.334mmol) was added and the resulting mixture was heated in a microwave reactor for at 120°C for 20mins. The reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (Horizons Biotage) eluting with 10% petroleum ether 40-60°C in DCM then 0-20% EtOAc in DCM to give the title compound (2.228g, 72%) as a solid. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.44 (m, 3H), 5.17 (d, 1H), 3.88 (bs, 2H), 3.08-3.00 (m, 1H), 2.32 (dt, 2H), 1.74 (s, 9H), 1.68-1.60 (m, 2H), 1.42 (s, 9H), 1.30-1.17 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.8, 154.7, 134.1, 131.9, 130.2, 128.9, 125.3, 107.3, 80.1, 61.9, 50.4, 42.4, 32.4, 28.6, 27.9; Mass Spectrum $M+H^+$ 464.

Example 87

2-*tert*-Butyl-4-{[1-(6-methoxypyridazin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.300g, 1.00mmol), 1-(6-methoxypyridazin-3-yl)piperidin-4-amine dihydrochloride (0.349g, 1.24mmol) and TEA (0.405g, 4.00mmol) was dissolved in dry DMF (10 ml) and heated in a microwave reactor at 120°C for 30 mins. The reaction mixture was diluted with water (200 ml) and extracted with EtOAc (200 ml). The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography using a 55:45 mixture of heptane and EtOAc as eluant, to give the title compound (0.232g, 49%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.46-7.41 (m, 3H), 6.92 (d, 1H), 6.79 (d, 1H), 5.2 (d, 1H), 4.00 (s, 3H), 3.93-3.87 (m, 2H), 3.17-3.08 (m, 1H), 2.53-2.45 (m, 2H), 1.77-1.71 (m, 2H), 1.72 (s, 9H),

1.44-1.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 159.6, 157.3, 133.8, 131.6, 129.9, 128.7, 125, 119.4, 119.1, 107, 61.6, 54.3, 50.1, 45.1, 31.6, 27.6; Mass Spectrum: M-H$^+$ 472.

Example 88

2-*tert*-Butyl-4-{[1-(6-chloropyridin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), 1-(6-chloropyridin-3-yl)piperidin-4-amine dihydrochloride (0.196g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified with preparative HPLC giving the title compound (0.022g, 8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92-7.87 (m, 1H), 7.55-7.48 (m, 2H), 7.48-7.41 (m, 3H), 7.13-7.03 (m, 2H), 5.24-5.18 (m, 1H), 3.45-3.35 (m, 2H), 3.13-3.01 (m, 1H), 2.39-2.29 (m, 2H), 1.82-1.71 (m, 2H), 1.73 (s, 9H), 1.52-1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 145.8, 141.7, 138.0, 134.1, 131.8, 130.2, 129.0, 126.6, 125.3, 124.1, 107.5, 61.9, 49.8, 47.8, 32.0, 27.8; Mass Spectrum: M-H$^+$ 475.

Example 89

4-[(1-Benzylpiperidin-4-yl)amino]-2-tert-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 24 from 1 equivalent 1-benzylpiperidie-4-amine, 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1 equivalent TEA with a reaction time of 30mins. The residue was purified by silica gel column chromatography (Horizons Biotage) using 35% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.132g, 58%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.7.47 (m, 2H), 7.46-7.42 (m, 3H), 7.31-7.26 (m, 2H), 7.26-7.21 (m, 3H), 5.20 (d, 1H), 3.35 (s, 2H), 2.99-2.90 (m, 1H), 2.67-2.62 (m, 2H), 1.74 (s, 9H), 1.71-1.56 (m, 4H), 1.44-1.33 (m, 2H); 13C NMR (125MHz $CDCl_3$): δ 159.9, 138.5, 134.2, 131.8, 129.9, 129.1, 128.8, 128.4, 127.3, 125.4, 106.7, 62.9, 61.7, 51.9, 50.3, 32.6, 27.8; Mass spectrum: M+H$^+$ 454.

Example 90

2-*tert*-Butyl-4-(ethylamino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), ethylamine hydrochloride (0.056g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction

mixture was purified by preparative HPLC to yield the title compound (0.099g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.46 (m, 2H), 7.43-7.38 (m, 3H), 5.21-5.12 (m, 1H), 2.89-2.80 (m, 2H), 1.72 (s, 9H), 1.01 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 135.2, 131.7, 129.7, 128.7, 125.4, 107.1, 61.7, 39.3, 27.8, 15.0; Mass Spectrum: M-H$^+$ 309.

Example 91

N~2~-(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-N~1~-[3-(difluoromethoxy)benzyl]glycinamide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), N-[3-(difluoromethoxy)benzyl]glycinamide (0.159g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.118g, 41%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.35 (m, 5H), 7.35-7.28 (m, 1H), 7.09-7.01 (m, 2H), 6.99-6.94 (m, 1H), 6.50 (t, 1H), 6.02-5.94 (m, 1H), 5.91-5.82 (m, 1H), 4.37-4.31 (m, 2H), 3.53-3.48 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 159.3, 139.9, 134.9, 131.5, 130.5, 130.2, 129.0, 125.1, 124.5, 119.4, 119.0, 116.0, 113.9, 109.9, 62.0, 46.8, 43.4, 27.8; Mass Spectrum: M-H$^+$ 494.

Example 92

2-*tert*-Butyl-5-phenyl-4-[(1-pyridin-2-ylpiperidin-4-yl)amino]isothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), 1-pyridin-2-ylpiperidin-4-amine dihydrochloride (0.173g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.175g, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08-8.03 (m, 1H), 7.50-7.44 (m, 2H), 7.41-7.32 (m, 4H), 6.55-6.47 (m, 2H), 5.28-5.20 (m, 1H), 4.02-3.93 (m, 2H), 3.11-3.00 (m, 1H), 2.41-2.30 (m, 2H), 1.73-1.60 (m, 2H), 1.67 (s, 9H), 1.36-1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 159.1, 148.0, 137.7, 134.2, 131.9, 130.1, 128.9, 125.4, 113.5, 107.5, 107.0, 61.7, 50.7, 44.1, 41.2, 32.0, 27.8; Mass Spectrum: M-H$^+$ 441.

Example 93

2-*tert*-Butyl-5-phenyl-4-[(1-pyridazin-3-ylpiperidin-4-yl)amino]isothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.240g, 0.80mmol), 1-pyridazin-3-ylpiperidin-4-amine (0.257g, 1.02mmol) and TEA (0.324g, 3.2mmol).was dissolved in dry DMF (10 ml) and heated in a microwave reactor at 120°C for 30 mins. The reaction mixture was diluted with water (300 ml) and extracted with EtOAc (2x150 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated and the residue was purified by silica gel column chromatography using EtOAc as eluant, to give the title compound (0.110g, 31%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55-8.52 (m, 1H), 7.55-7.50 (m, 2H), 7.47-7.42 (m, 3H), 7.19-7.14 (m, 1H), 6.85-6.82 (m, 1H), 5.21 (d, 1H), 4.17-4.11 (m, 2H), 3.22-3.13 (m, 1H), 2.60-2.52 (m, 2H), 1.80-1.73 (m, 2H), 1.72 (s, 9H), 1.42-1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 143.1, 133.8, 131.6, 129.9, 128.7, 127.4, 125, 112.8, 107.2, 61.6, 50.1, 43.6, 31.7, 27.5; Mass Spectrum: M-H$^+$ 442.

Example 94

2-*tert*-Butyl-4-{[1-(5-fluoropyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), 1-(5-fluoropyridin-2-yl)piperidin-4-amine dihydrochloride (0.155g, 0.58mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.153g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01-7.95 (m, 1H), 7.56-7.49 (m, 2H), 7.48-7.39 (m, 3H), 7.23-7.16 (m, 1H), 6.56-6.48 (m, 1H), 5.25-5.15 (m, 1H), 3.98-3.86 (m, 2H), 3.17-3.04 (m, 1H), 2.47-2.36 (m, 2H), 1.80-1.64 (m, 2H), 1.72 (s, 9H), 1.43-1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 156.1, 154.7, 152.7, 134.8, 134.6, 134.1, 131.9, 130.1, 128.9, 125.3, 108.3, 107.3, 61.8, 50.5, 45.0, 32.0, 27.8; Mass Spectrum: M-H$^+$ 459.

Example 95

2-*tert*-Butyl-4-{[3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (150 mg, 0.5 mmol), 3-(3,5-dimethyl-pyrazol -1-yl)-propylamine tartrate (167 mg, 0.55 mmol) were mixed in MeCN (3 ml). Triethylamine (0.23 ml, 1.65 mmol) was added and the mixture was heated in a

microwave reactor at 120°C for 15 mins. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography (ISOLUTE SI, 20g/70ml), eluting with DCM and then MeOH/DCM (1:99), to give the title compound (195 mg, 94%). ^{1}H NMR (400 MHz, CDCl3): δ 1.70 (s, 9H), 1.72-1.79 (m, 2H), 2.05 (s, 3H), 2.18 (s, 3H), 2.81-2.86 (m 2H), 3.79 (t, 2H), 5.71 (bs, 2H), 7.37-7.46 (m, 5H); ^{13}C NMR (100 MHz, CDCl3): δ 10.8, 13.4, 27.5, 29.2, 41.5, 45.4, 61.3, 105.1, 106.8, 125.0, 128.4, 129.4, 131.4, 135.0, 138.5, 147.7, 159.3; Mass Spectrum: M+H$^+$ 417.

Example 96

2-*tert*-Butyl-4-{[1-(5-chloropyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), 1-(5-chloropyridin-2-yl)piperidin-4-amine dihydrochloride (0.196g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.124g, 45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06-8.02 (m, 1H), 7.55-7.49 (m, 2H), 7.47-7.41 (m, 3H), 7.39-7.33 (m, 1H), 6.52-6.45 (m, 1H), 5.24-5.14 (m, 1H), 4.02-3.93 (m, 1H), 3.18-3.06 (m, 1H), 2.49-2.39 (m, 2H), 1.78-1.66 (m, 2H), 1.72 (s, 9H), 1.39-1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 157.4, 146.3, 137.5, 134.1, 131.9, 130.2, 128.9, 125.3, 120.5, 108.2, 107.3, 61.9, 50.5, 44.3, 32.0, 27.8; Mass Spectrum: M-H$^+$ 475.

Example 97

2-*tert*-Butyl-5-phenyl-4-({1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)isothiazol-3(2H)-one 1,1-dioxide

2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.175g, 0.58mmol), 1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-amine dihydrochloride (0.220g, 0.69mmol) and TEA (0.23g, 2.31mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 130°C for 30 mins. The reaction mixture was purified by preparative HPLC to yield the title compound (0.112g, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28-8.23 (m, 1H), 7.59-7.52 (m, 2H), 7.51-7.44 (m, 3H), 6.79-6.74 (m, 1H), 6.74-6.70 (m, 1H), 5.27-5.17 (m, 1H), 4.17-4.07 (m, 2H), 3.24-3.13 (m, 1H), 2.57-2.48 (m, 2H), 1.83-1.69 (m, 2H), 1.75 (s, 9H), 1.42-1.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 149.3, 134.1, 131.9, 130.2, 129.0, 125.3, 108.5, 107.4, 102.9, 61.9, 50.5, 43.9, 32.0, 27.8; Mass Spectrum: M-H$^+$ 509.

Example 98

2-*tert*-Butyl-4-(tert-butylamino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 24 from *tert*-butylamine and 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide at 140°C for 1.5h. The residue was purified by silica gel column chromatography (Horizons Biotage) using 0-5% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.029g, 17%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): δ .54-7.50 (m, 2H), 7.48-7.44 (m, 3H), 5.53 (s, 1H), 1.74 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): 160.9, 133.8, 133.5, 130.3, 129.1, 126.8, 106.6, 61.8, 52.2, 30.1, 27.8; Mass Spectrum: $M+H^+$ 337.

Example 99

2-{2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate (150mg, 0.313mmol) was dissolved in dry MeCN (3mL) under nitrogen atmosphere. 2-Hydroxyphenyl methanesulfonate (65mg, 0.345mmol) was added followed by potassium carbonate (217mg, 1.567mmol). The reaction mixture was heated in a microwave reactor at 120°C for 15 mins.. Potassium carbonate was filtered off and the reaction mixture was evaporated to dryness in a vacuum centrifuge. The crude product was purified by preparative HPLC affording the title compound (94mg, 58.5%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.71 (s, 9H), 3.19 (s, 3H), 3.26 (q, 2H), 3.92 (t, 2H), 5.86 (t, 1H), 6.86 (d, 1H), 6.99 (t, 1H), 7.22 (t, 1H), 7.28 (d, 1H), 7.42-7.45 (m, 3H), 7.49-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.82, 38.53, 43.28, 61.78, 67.18, 108.11, 114.66, 122.30, 124.66, 125.15, 128.54, 129.08, 130.04, 131.69, 135.27, 138.61, 150.49, 159.51; Mass Spectrum: $M+H^+$ 494.8.

Example 100

***tert*-Butyl 3-({2-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}thio)pyrrolidine-1-carboxylate**

2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate (150mg, 0.313mmol) was dissolved in dry MeCN (3mL) under nitrogen atmosphere. *tert*-Butyl 3-mercaptopyrrolidine-1-carboxylate (70mg, 0.345mmol) was

added followed by potassium carbonate (217mg, 1.567mmol). The reaction mixture was heated in a microwave reactor at 120°C for 15 mins. Potassium carbonate was filtered off and the reaction ixture was evaporated to dryness in a vacuumcentrifuge. The crude product was purified by preparative HPLC affording the title compound (134mg, 83.4%). The product is a mixture of cis and trans isomers. ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.47 (s, 9H), 1.73 (s, 10H), 2.05 (s, 1H), 2.46-2.51 (m, 2H), 2.88 (bs, 1H), 3.01-3.13 (m, 3H), 3.29 (s, 1H), 3.41-3.57 (m, 2H), 5.65 (bs, 1H), 7.43-7.46 (m, 3H), 7.49-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.83, 28.73, 31.29, 32.33, 32.86, 41.74, 42.41, 43.23, 44.86, 45.09, 52.27, 52.53, 61.86, 79.79, 108.04, 125.15, 129.04, 130.04, 131.65, 134.81, 154.41, 159.66; Mass Spectrum: $M+H^+$ 509.9.

Example 101

Methyl 2-{2-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}benzoate

2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate (150mg, 0.313mmol) was dissolved in dry MeCN (3mL) under nitrogen atmosphere. Methyl salicylate (52mg, 0.345mmol) was added followed by potassium carbonate (217mg, 1.567mmol). The reaction mixture was heated in a microwave reactor at 120°C for 20 mins. Potassium carbonate was filtered off and the reaction mixture was evaporated to dryness in a vacuum centrifuge. The crude product was purified by preparative HPLC affording the title compound (9mg, 6%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.74 (s, 9H), 3.27 (q, 2H), 3.97-4.00 (m, 5H), 6.17 (t, 1H), 6.86 (d, 1H), 7.05 (t, 1H), 7.44-7.48 (m, 4H), 7.52-7.56 (m, 2H), 7.85 (dd, 1H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.85, 43.53, 52.52, 61.69, 67.49, 107.84, 114.40, 121.12, 121.69, 125.42, 129.00, 129.85, 131.69, 132.27, 133.85, 135.56, 158.01, 159.56, 166.79; Mass Spectrum: $M+H^+$ 459.0.

Example 102

2-*tert*-Butyl-5-phenyl-4-{[2-(pyridin-3-yloxy)ethyl]amino}isothiazol-3(2H)-one 1,1-dioxide

2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate (150mg, 0.313mmol) was dissolved in dry MeCN (3mL) under nitrogen atmosphere. Pyridin-3-ol (33mg, 0.345mmol) was added followed by potassium carbonate (217mg, 1.567mmol). The reaction mixture was heated in a microwave reactor at

120°C for 15 mins. Potassium carbonate was filtered off and the reaction mixture was evaporated to dryness in a vacuum centrifuge. The crude product was purified by preparative HPLC affording the title compound (46mg, 35.7%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.74 (s, 9H), 3.30 (q, 2H), 3.92 (t, 2H), 5.64 (t, 1H), 7.12-7.14 (m, 1H), 7.22-7.24 (m, 1H), 7.46-7.48 (m, 3H), 7.53-7.55 (m, 2H), 8.26-8.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.84, 43.32, 61.90, 66.37, 108.51, 121.55, 124.15, 125.03, 129.09, 130.10, 131.69, 135.11, 137.90, 143.23, 154.51, 159.64; Mass Spectrum: $M+H^+$ 402.1.

Example 103

4-{2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate (150mg, 0.313mmol) was dissolved in dry MeCN (3mL) under nitrogen atmosphere. 4-Hydroxyphenyl methanesulfonate (65mg, 0.345mmol) was added followed by potassium carbonate (217mg, 1.567mmol). The reaction mixture was heated in a microwave reactor at 120°C for 15 mins. Potassium carbonate was filtered off and the reaction mixture was evaporated to dryness in a vacuum centrifuge. The crude product was purified by preparative HPLC affording the title compound (61mg, 38.5%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.73 (s, 9H), 3.11 (s, 3H), 3.23-3.27 (m, 2H), 3.83-3.86 (m, 2H), 5.65 (bs, 1H), 6.83 (d, 2H), 7.20 (d, 2H), 7.43-7.46 (m, 3H), 7.50-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.83, 37.34, 43.30, 61.85, 66.50, 108.27, 115.77, 123.48, 125.07, 129.07, 130.06, 131.68, 135.18, 143.35, 157.21, 159.65; Mass Spectrum: $M+NH_4^+$ 511.8.

Example 104

4-({4-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}methyl)benzonitrile

A mixture of 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) (0.100g, 0.275mmol), 4-(bromomethyl)benzonitrile (0.054g, 0.275mmol), 1-benzyl-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine on polystyrene (0.055g, 0.413mmol) in DMF (2ml) was heated in a microwave reactor at 150°C for 7mins. The reaction mixture was filtered, evaporated to dryness and the residue was purified by preperative HPLC to give the title compound (0.040g, 30%); ^{1}H NMR (500MHz $CDCl_3$): δ 7.59 (d, 2H), 7.52-7.49 (m, 2H), 7.48-7.42 (m, 3H), 7.37 (d, 2H), 5.21 (d, 1H), 3.41 (s, 2H),

3.01-2.90 (m, 1H), 2.65-2.56 (m, 2H), 1.74 (s, 9H), 1.69-1.60 (m, 4H), 1.44-1.34 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 144.5, 134.2, 132.3, 131.9, 129.9, 129.4, 128.9, 125.4, 119.1, 111.1, 106.9, 62.3, 61.8, 51.9, 50.1, 32.5, 27.8; Mass Spectrum M+H$^+$ 479.

Example 105

2-*tert*-Butyl-5-phenyl-4-({1-[2-(trifluoromethyl)benzoyl]piperidin-4-yl}amino)isothiazol-3(2H)-one 1,1-dioxide

A mixture of 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) (0.100g, 0.275mmol), 2-(trifluoromethyl)benzoyl chloride (0.049ml, 0.330mmol) and 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene (0.600g, 1.376mmol) in DCM (2ml) was stirred at rt for 17h. The mixture was filtered, evaporated to dryness and the residue was purified by preperative HPLC to give the title compound (0.053g, 36%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.68 (t, 1H), 7.61-7.42 (m, 6h), 7.26 (d, 1H), 7.18 (d, 1H), 5.21 (d, 1H), 4.61-4.46 (m, 1h), 3.24-3.10 (m, 2H), 2.54-2.38 (m, 2H), 1.88-1.78 (m, 1H), 1.76-1.48 (10H), 1.44-1.32 (m, 1H), 1.26-1.10 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 167.4, 167.3, 159.8, 159.7, 134.8, 133.9, 133.8, 132.5, 132.3, 131.9, 131.7, 130.4, 130.2, 129.5, 129.0, 128.9, 127.3, 127.0, 126.9, 125.3, 125.1, 107.8, 107.5, 61.9, 50.3, 50.1, 45.7, 45.5, 41.2, 40.3, 40.1, 32.5, 32.1, 31.9, 31.8, 27.8; Mass Spectrum: M-H$^+$ 534

Example 106

Methyl 3-({4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}methyl)benzoate

The title compound was prepared as described for Example 104 from methyl 3-(bromomethyl)benzoate and 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) to give the title compound (0.101g, 48%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): δ 7.95-7.87 (m, 2H), 7.54-7.32 (m, 7H), 5.20 (d, 1H), 3.92 (s, 3H), 3.38 (s, 2H), 3.00-2.80 (m, 1H), 2.66-2.58 (m, 2H), 1.80-1.54 (m, 13H), 1.42-1.30 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 167.4, 159.9, 139.1, 134.3, 133.6, 131.8, 130.4, 130.2, 129.9, 128.8, 128.6, 125.4, 106.8, 62.5, 61.8, 52.3, 51.9, 50.2, 32.5, 27.8; Mass Spectrum: M+H$^+$ 512.

Example 107

2-*tert*-Butyl-4-({1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 105 from 2-chloronicotinyl chloride and 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) to give the title compound (0.030g, 22%). ^{1}H NMR (500MHz $CDCl_3$): δ 8.46-8.42 (m, 1H), 7.62 (d, 1H), 7.58-7.44 (m, 5H), 7.37-7.26 (m, 1H), 7.52 (dd, 1H), 3.30-3.10 (m, 2H), 2.73-2.40 (m, 5H), 1.90-1.80 (m, 1H), 1.74 (s, 9H), 1.68-1.58 (m, 2H), 1.54-1.10 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 165.2, 165.1, 159.7, 159.6, 150.5, 150.3, 147.3, 137.0, 136.9, 133.9, 133.8, 132.3, 132.1, 131.9, 131.7,l 130.4, 130.2, 129.1, 128.9, 125.3, 125.0, 123.0, 122.9, 108.1, 107.7, 61.9, 50.3, 49.9, 45.7, 44.9, 40.4, 40.2, 32.8, 32.7, 32.0, 31.9, 27.8; Mass Spectrum: M-H$^+$ 503.

Example 108

2-*tert*-Butyl-4-({1-[(5-methylisoxazol-3-yl)methyl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 104 from 3-(bromomethyl)-5-methylisooxazole and 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) to give the title compound (0.021g, 17%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.48-7.42 (m, 3H), 5.92 (s, 1H), 5.18 (d, 1H), 3.40 (s, 2H), 2.98-2.88 (m, 1H), 2.70-2.62 (m, 2H), 2.40 (s, 3H), 1.74 (m, 9H), 1.79-1.60 (m, 4H), 1.42-1.32 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 169.7, 161.7, 159.9, 134.2, 131.8, 130.1, 128.9, 125.3, 106.9, 101.8, 61.8, 53.4, 52.0, 50.1, 32.5, 27.8, 12.5; Mass Spectrum M+H$^+$ 459.

Example 109

4-[(1-Benzoylpiperidin-4-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

A mixture of 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) (0.150mg, 0.413mmol), benzoic acid (0.055g, 0.454mmol), EDC (0.087g, 0.454mmol), HOBt (0.061g, 0.454mmol) and TEA (0.120ml, 0.825mmol) in THF (3ml) was stirred at rt for 3.5h. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 50% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.136g, 71%) as a solid. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.42 (m, 5H), 7.42-7.35 (m, 2H), 7.32-7.29 (m, 1H), 5.21 (d, 1H), 4.48 (bs, 1H), 3.56 (bs, 1H), 3.24-3.12 (m, 1H), 2.58-2.44 (m, 2H), 1.90-1.64 (bs,

2H), 1.74 (s, 9H), 1.48-1.16 (bs, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 170.6, 159.7, 135.7, 133.9, 131.8, 130.2, 130.0, 128.9, 128.7, 126.9, 125.2, 107.7, 61.9, 50.4, 27.8; Mass Spectrum: M+H$^+$ 468.

Example 110

2-*tert*-Butyl-5-phenyl-4-{[1-(phenylacetyl)piperidin-4-yl]amino}isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 105 from phenylacetic chloride and 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) to give the title compound (0.103g; 78%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.47 (m, 2H), 7.47-7.41 (m, 3H), 7.34-7.29 (m, 2H), 7.27-7.23 (m, 1H), 7.18 (d, 2H), 5.12 (d, 1H), 4.43-4.26 (m, 1H), 3.70-3.61 (m, 3H), 3.11-3.02 (m, 1H), 2.55-2.47 (m, 1H), 2.28-2.20 (m, 1H), 1.90-1.65 (m, 11H), 1.54-1.47 (m, 1H), 1.19 (dq, 1H), 0.91 (dq, 1H); ^{13}C δ NMR (125MHz $CDCl_3$): 169.5, 159.7, 135.0, 133.9, 131.8, 130.2, 129.0, 128.9, 128.6, 127.2, 125.2, 107.5, 61.9, 50.2, 44.6, 41.3, 41.2, 40.4, 32.6, 32.1, 27.8; Mass Spectrum: M+H$^+$ 482.

Example 111

2-*tert*-Butyl-4-{[1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 105 from 2-chloride-6-methylisonicotinoyl chloride and 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) using DMAP as catalyst and DMF as solvent. EtOAc was added to the reaction mixture, and it was washed with brine, evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 50% EtOAc in petroleum ether 40-60°C as eluent to give the title compound (0.037g, 26%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.43 (m, 3H), 7.02 (s, 1H), 6.96 (s, 1H), 5.21 (d, 1H), 4.48-4.38 (m, 1H),. 3.46-3.36 (m, 1H), 3.24-3.14 (m, 1H), 2.62-2.40 (m, 5H), 1.90-1.80 (m, 1H), 1.74 (s, 9H), 1.70-1.60 (m, 1H), 1.44-1.32 (m, 1H), 1.30-1.18 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 166.7, 160.7, 159.7, 151.3, 146.6, 133.9, 131.8, 130.3, 129.0, 125.2, 119.3, 118.6, 107.9, 61.9, 50.1, 45.8, 41.1, 40.7, 32.9, 31.9, 27.8, 24.5; Mass Spectrum: M+H$^+$ 517.

Example 112

4-({4-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}carbonyl)benzonitrile

The title compound was prepared as described for Example 105 from 4-cyanobenzoyl chloride and 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) using DMF as solvent. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (Horizons Biotage) using 50% EtOAc in petroleum ether 40-60°C as eluent. The product containing fractions were evaporated, dissolved in DCM, washed through a cation exchange column and evaporated to give the title compound (0.015g, 11%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.70 (d, 1H), 7.55-7.50 (m, 2H), 7.49-7.40 (m, 5H), 5.21 (d, 1H), 4.52-4.40 (m, 1H), 3.50-3.36 (m, 1H), 3.24-3.14 (m, 2H), 2.62-2.44 (m, 2H), 1.92-1.78 (m, 1H), 1.74 (s, 9H), 1.67-1.54 (m, 2H), 1.48-1.16 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 168.5, 159.7, 140.1, 133.9, 132.7, 131.8, 130.3, 129.0, 127.7, 125.2, 118.2, 113.9, 107.9, 61.9, 50.1, 46.0, 40.9, 32.9, 32.1, 27.8; M+H$^+$ 493.

Exampel 113

2-*tert*-Butyl-4-{[1-(3,4-difluorobenzoyl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared as described for Example 105 from 3,4-difluorobenzoyl chloride and 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) to give the title compound (0.033g, 24%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.48-7.42 (m, 3H), 7.22-7.14 (m, 2H), 7.10-7.04 (m, 1H), 5.23 (d, 1H), 4.40 (bs, 1H), 3.58 (bs, 1H), 3.22-3.12 (m, 1H), 2.58-2.46 (m, 2H), 1.80-1.60 (m, 11H), 1.42-1.14 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 168.3, 159.7, 152.6, 152.4, 151.6, 151.4, 150.6, 150.4, 149.6, 149.4, 133.9,132.5, 131.8, 130.3, 129.0, 125.2, 123.7, 117.9, 117.8, 116.9, 116.8, 107.8, 61.9, 50.2, 46.0, 32.5, 27.8; Mass Spectrum: M-H$^+$ 502.

Example 114

4-{2-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

A mixture of 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.15g, 0.52mmol), 4-(2-aminoethyl)phenyl methanesulfonate (0.14g, 0.63mmol) and TEA (0.07g, 0.68mmol) in MeCN (1.5ml) was heated in a microwave reactor at 120°C for 35mins. 4-(2-Aminoethyl)phenyl methanesulfonate (0.07g) was added to the mixture, and it was heated in a

microwave reactor at 120°C for 20mins. The reaction mixture was evaporated and the crude product was purified by flash column chromatography using hexane and EtOAc, 80:20–30:70, as eluant to yield the title compound (0.21g, 85%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.57-1.59 (m, 6H), 2.50-2.61 (m, 2H), 3.12-3.16 (m, 5H), 4.39-4.42 (m, 1H), 5.23 (brm, 1H), 6.80-6.83 (m, 2H), 7.12-7.15 (m, 2H), 7.48-7.54 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$): δ 14.4, 20.4, 35.5, 37.6, 45.0, 47.8, 107.8, 122.4, 125.2, 129.1, 130.1, 130.3, 131.8, 135.2, 137.0, 148.2, 158.6; Mass Spectrum: M-H$^+$ 463.

Example 115

4-{2-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzenesulfonamide

A mixture of 4-chloro-2-isopopyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.16g, 0.56mmol), 4-(2-aminoethyl)benzenesulfonamide (0.14g, 0.67mmol) and TEA (0.07g, 0.73mmol) in MeCN (1.5ml) was heated in a microwave reactor at 120°C for 15mins. The reaction mixture was evaporated and THF was added to the residue. The mixture was filtrated and the eluant was concentrated. The residue was recrystallized from THF and hexane to yield the title compound (0.19g, 74%). ^{1}H NMR (500MHz, THF): δ 1.53 (d, 6H), 2.62 (t, 2H), 3.16-3.20 (m, 2H), 4.30-4.38 (m, 1H), 6.38 (s, 1H), 6.63 (t, 1H), 6.87 (d, 2H), 7.48-7.51 (m, 3H), 7.56-7.58 (m, 2H), 7.68 (d, 2H); ^{13}C NMR (125MHz, THF): δ 19.4, 35.6, 44.7, 47.0, 106.9, 126.3, 126.5, 128.6, 128.8, 129.4, 132.0, 135.6, 142.3, 143.3, 158.5; Mass Spectrum: M+H$^+$ 450.

Example 116

4-{2-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

A mixture of 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.15g, 0.52mmol), 4-(2-aminoethyl)benzonitrile (0.09g, 0.63mmol) and TEA (0.07g, 0.68mmol) in MeCN (1.5ml) was heated in a microwave reactor at 120°C for 35mins. 4-(2-Aminoethyl)benzonitrile (0.04g) was added to the reaction mixture, and it was heated in a microwave reactor at 120°C for 20mins. The reaction mixture was evaporated and the crude product was purified by flash column chromatography using hexane and EtOAc ,80:20–50:50, as eluant, to yield the title compound (0.14g, 67%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.57 (d, 6H), 2.63 (t, 2H), 3.15-3.19 (m, 2H), 4.37-4.43 (m, 1H), 5.46 (brm, 1H), 6.86 (d, 2H),

7.45-5.55 (m, 7H); ^{13}C NMR (125MHz, $CDCl_3$): δ 20.4, 36.2, 44.5, 47.9, 107.8, 111.0, 118.9, 125.2, 129.1, 129.5, 130.1, 131.8, 132.7, 135.1, 143.1, 158.6; Mass Spectrum: M-H$^+$ 394.

Example 117

3-{2-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (150mg, 0.525mmol) was dissolved in dry DMF (1mL) under nitrogen atmosphere. 3-(2-Aminoethyl)benzonitrile (78mg, 0.530mmol) was added followed by TEA (53mg, 0.525mmol) and the reaction mixture was heated in a microwave reactor for at 120°C for 20mins.. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$-solution, dried over Na_2SO_4, filtered and evaporated. The crude product was purified on a Biotage Horizon HPFC system using Heptane and EtOAc as eluant affording the title compound (118mg, 56.3%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, 6H), 2.60 (t, 2H), 3.17 (q, 2H), 4.37-4.46 (m, 1H), 5.49 (bs, 1H), 6.88 (s, 1H), 7.02 (d, 1H), 7.30-7.34 (m, 1H), 7.47-7.57 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.38, 35.75, 44.70, 47.90, 107.72, 113.00, 118.70, 125.17, 129.19, 129.67, 130.36, 130.77, 131.95, 132.20, 133.23, 135.11, 139.03, 158.60; Mass Spectrum: M+H$^+$ 396.1.

Example 118

4-({1-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-yl}amino)-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (150mg, 0.525mmol) was dissolved in dry DMF (1mL) under nitrogen atmosphere. 1-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-amine (133mg, 0.530mmol) was added followed by TEA (53mg, 0.525mmol) and the reaction mixture was heated in a microwave reactor for at 120°C for 20 mins. The mixture was diluted with EtOAc, washed with saturate aqueous $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The crude product was purified on a Biotage Horizon HPFC system using Heptane and EtOAc as eluant affording the title compound (223g, 84.0%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60 (d, 6H), 4.01-4.06 (m, 3H), 4.10-4.15 (m, 2H), 4.40-4.48 (m, 1H), 5.62 (bs, 1H), 7.51 (s, 5H), 7.59 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.38, 44.61, 48.06, 59.87, 109.52, 115.56, 117.98 (q, J_{C-F}=33.6Hz), 124.42, 124.75, 129.29, 130.48, 131.49, 134.49, 135.16, 143.70, 156.92, 158.26; Mass Spectrum: M+H$^+$ 501.1.

Example 119

2-*tert*-Butyl-4-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

4-[(2-Aminoethyl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (0.088g, 0.27mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine (0.065g, 0.30mmol) and TEA (0.055g, 0.54mmol) was dissolved in dry DMF (3 ml) and heated in a microwave reactor at 120 °C for 25 mins. The reaction mixture was extracted with EtOAc (75 ml) and the organic phases were washed with water (3x50 ml), dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography using petroleum ether and EtOAc (85:15) as eluant, to give the title compound (0.052g, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.3-8.25 (m, 1H), 7.67-7.62 (m, 2H), 7.49-7.43 (m, 2H), 7.43-7.35 (m, 3H), 6.47-6.41 (m, 1H), 5.47-5.41 (m, 1H), 3.52 (q, 2H), 3.09 (q, 2H), 1.7 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 155.7, 143.7, 143.6, 135.5, 133.2, 133.1, 131.5, 129.4, 128.5, 125, 124.6, 122.4, 116.8, 116.6, 115, 107.1, 61.4, 45.4, 40.9, 27.5; Mass Spectrum: M-H$^+$ 503.

Example 120

2-{2-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

2-[(2-Isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate (200mg, 0.431mmol) was dissolved in dry MeCN (4mL) under nitrogen atmosphere. 2-Hydroxyphenyl methanesulfonate (89mg, 0.474mmol) was added followed by potassium carbonate (297mg, 2.152mmol). The reaction mixture was heated in a microwave reactor for 15 mins at 120°C. Potassium carbonate was filtered off and the reaction mixture was concentrated and redissolved in EtOAc. The mixture was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The residue was purified on a Horizon TM flash system using Heptane and EtOAc as eluant and TEA as additative and then purified by column chromatography (ISOLUTE SI, (5g)) using DCM as eluant to afford the title compound (31mg, 15%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.59 (d, 6H), 3.22 (s, 3H), 3.31 (q, 2H), 3.96 (t, 2H), 4.38-4.46 (m, 1H), 5.88 (t, 1H), 6.89 (d, 1H), 7.02 (t, 1H), 7.23-7.30 (m, 2H), 7.46-7.48 (m, 3H), 7.53-7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 20.38, 38.57,

43.36, 47.85, 67.23, 108.08, 114.71, 122.38, 124.59, 125.14, 128.55, 129.15, 130.09, 131.63, 135.62, 138.64, 150.55, 158.40; Mass Spectrum: M+H$^+$ 481.1.

Examples 121 to 139 were prepared from 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and the appropriate amine in analogy with the descriptions for Examples 1, 4, 15, 23, 24, 49, 76-82, 84-88, 90-97. Starting material is either commercially available or can be prepared as described or in analogy with methods described in the section for synthesis of starting material and intermediates or can be prepared according to methods known to person skilled in the art.

Example 121

2-*tert*-Butyl-5-phenyl-4-({2-[2-(trifluoromethoxy)phenyl]ethyl}amino)isothiazol-3(2H)-one 1,1-dioxide

Commercially available 2-[2-(trifluoromethoxy)phenyl]ethanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.56-7.50 (m, 2H), 7.49-7.43 (m, 3H), 7.29-7.12 (m, 3H), 6.77-6.73 (m, 1H), 5.40-5.33 (m, 1H), 3.19-3.11 (m, 2H), 2.72-2.65 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.6, 147.8, 134.8, 131.7, 130.9, 130.0, 129.8, 128.8, 128.5, 127.0, 125.1, 120.7, 107.7, 61.6, 43.6, 30.1, 27.7; Mass Spectrum: M-H$^+$ 469.

Example 122

4-[(1-Benzylpyrrolidin-3-yl)amino]-2-tert-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 1-benzylpyrrolidin-3-amine was also used as starting material to give the title compound. ^{1}H NMR(500MHz $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.46-7.40 (m, 3H), 7.35-7.30 (m, 2H), 7.30-7.24 (m, 3H), 5.53 (d, 1H), 3.68-3.60 (m, 1H), 3.52 (dd, 2H), 2.74-2.68 (m, 1H), 2.45 (dd, 1H), 2.30-2.22 (m, 1H), 2.22-2.14 (m, 1H), 1.80-1.64 (m, 10H), 1.60-1.52 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 138.5, 134.5, 131.9, 129.8, 128.9, 128.6, 127.4, 125.2, 107.1, 61.7, 60.8, 59.9, 52.7, 52.4, 33.1, 27.8; Mass Spectrum: M+H$^+$ 440.

Example 123

N -Benzyl-N^2-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinamide

N^1-Benzylglycinamide was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.48-7.22 (m, 10H), 6.04-5.97 (m, 1H), 5.78-5.71 (m, 1H), 4.39 (d, 2H), 3.52 (d, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 166.9, 159.2, 137.4, 134.9, 131.4, 130.0, 129.0, 128.9, 128.2, 128.1, 124.5, 109.7, 61.8, 46.7, 43.9, 41.0, 27.7; Mass Spectrum: M-H^+ 428.

Example 124

2-*tert*-Butyl-5-phenyl-4-[(2-pyridin-2-ylethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

Commercially available 2-pyridin-2-ylethanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.57-8.50 (m, 1H), 7.61-7.48 (m, 3H), 7.47-7.38 (m, 3H), 7.18-7.10 (m, 1H), 6.95-6.88 (m, 1H), 6.32-6.22 (m, 1H), 3.30-3.21 (m, 2H), 2.84-2.77 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.7, 158.3, 149.5, 136.8, 135.3, 131.6, 129.5, 128.7, 125.4, 123.3, 121.9, 106.8, 61.4, 43.4, 36.7, 27.7; Mass Spectrum: M-H^+ 386.

Example 125

2-*tert*-Butyl-4-{[2-(2-chlorophenyl)ethyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 2-(2-chlorophenyl)ethanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.55-7.49 (m, 2H), 7.49-7.43 (m, 3H), 7.34-7.30 (m, 1H), 7.20-7.10 (m, 2H), 6.78-6.74 (m, 1H), 5.42-5.35 (m, 1H), 3.23-3.15 (m, 2H), 2.79-2.71 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.7, 135.3, 134.9, 134.1, 131.6, 130.8, 129.8, 129.8, 128.8, 128.5, 127.1, 125.2, 107.6, 61.6, 43.3, 41.0, 33.7, 27.7; Mass Spectrum: M-H^+ 419.

Example 126

2-*tert*-Butyl-5-phenyl-4-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)isothiazol-3(2H)-one 1,1-dioxide

Commercially available 2-[3-(trifluoromethyl)phenyl]ethanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.55-7.40 (m, 6H), 7.33-7.27 (m, 1H), 6.98-6.93 (m, 1H), 6.91-6.88 (m, 1H), 5.62-5.55 (m, 1H), 3.16-3.10 (m, 2H), 2.62-2.56 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.8, 138.6, 134.9, 132.2,

131.9, 131.2, 130.9, 130.2, 130.0, 129.2, 129.0, 125.4, 125.4, 125.2, 123.8, 123.8, 123.1, 107.5, 61.8, 44.8, 41.1, 36.0, 27.8; Mass Spectrum: M-H^+ 453.

Example 127

2-*tert*-Butyl-5-phenyl-4-[(4-{[4-(trifluoromethyl)phenyl]thio}cyclohexyl)amino]isothiazol-3(2H)-one 1,1-dioxide

4-{[4-(Trifluoromethyl)phenyl]thio}cyclohexanamine was also used as starting material to give the title compound as a mixture of cis and trans isomeres. ^{1}H NMR (500MHz, $CDCl_3$): δ 0.87-0.95 (m, 2H), 1.12-1.20 (m, 2H), 1.42-1.92 (m, 30H), 2.00 (s, 2H), 2.88-3.09 (m, 3H), 3.37-3.40 (m, 1H), 5.15 (d, 1H), 5.31 (d, 1H), 7.35-7.38 (m, 4H), 7.42-7.52 (m, 14H); ^{13}C NMR (125MHz, $CDCl_3$): δ 27.83, 28.65, 31.43, 33.02, 43.22, 44.30, 50.35, 51.25, 61.79, 106.92, 124.28 (q, J(C-F)=272.2Hz), 125.26, 125.44, 125.97, 128.84, 128.90, 129.94, 130.13, 130.18, 130.57, 131.85, 131.89, 134.09, 134.19, 140.20, 140.67, 159.96; Mass Spectrum: M-H^+ 536.9.

Example 128

2-*tert*-Butyl-5-phenyl-4-({1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)isothiazol-3(2H)-one 1,1-dioxide

1-[5-(Trifluoromethyl)pyridin-2-yl]piperidin-4-amine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.38-8.32 (m, 1H), 7.63-7.51 (m, 3H), 7.51-7.43 (m, 3H), 6.62-6.54 (m, 1H), 5.21 (d, 1H), 4.21-4.14 (m, 2H), 3.25-3.15 (m, 1H), 2.60-2.50 (m, 2H), 1.82-1.70 (m, 2H), 1.74 (s, 9H), 1.4-1.29 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.7, 145.6, 134.8, 134.0, 131.8, 130.1, 128.9, 125.2, 107.4, 105.9, 61.8, 50.3, 43.5, 31.9, 27.7; Mass Spectrum: M-H^+ 509.

Example 129

***tert*-Butyl 3-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}azetidine-1-carboxylate**

tert-Butyl 3-(2-aminoethoxy)azetidine-1-carboxylate was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.53-7.48 (m, 2H), 7.47-7.42 (m, 3H), 5.57-5.51 (m, 1H), 4.16-4.10 (m, 1H), 4.07-4.00 (m, 2H), 3.80-3.74 (m, 2H), 3.31-3.26 (m, 2H), 3.06-3.00 (m, 2H), 1.74 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.6,

156.3, 135.1, 131.6, 129.8, 128.8, 125.0, 107.9, 79.8, 68.2, 66.5, 61.7, 56.4, 43.6, 28.5, 27.7; Mass Spectrum: M-H^+ 480.

Example 130

2-*tert*-Butyl-4-[(2,2-dimethylpropyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 2,2-dimethylpropan-1-amine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.51-7.46 (m, 2H), 7.46-7.41 (m, 3H), 5.34-5.26 (m, 1H), 2.62 (d, 2H), 1.75 (s, 9H), 0.81 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.9, 135.5, 131.8, 129.6, 128.7, 125.3, 106.6, 61.6, 55.3, 31.9, 27.7, 27.0; Mass Spectrum: M-H^+ 351.

Example 131

Methyl ({[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetyl}amino)acetate

Commercially available methyl glycylglycinate was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.48 (m, 2H), 7.48-7.44 (m, 3H), 6.03 (t, 1H), 5.98 (t, 1H), 4.00 (d, 2H), 3.78 (s, 3H), 3.56 (d, 2H), 1.74 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 167.5, 159.3, 134.9, 131.6, 130.2, 129.1, 124.5, 109.9, 61.9, 52.8, 46.7, 41.4, 27.8; Mass Spectrum: M+H^+ 410.

Example 132

2-*tert*-Butyl-4-[(1-methylpiperidin-4-yl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 1-methylpiperidin-4-amine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.42 (m, 3H), 5.19 (d, 1H), 2.96-2.86 (m, 1H), 2.63-2.58 (m, 2H), 2.15 (s, 3H), 1.74 (s, 9H), 1.68-1.52 (m, 4H), 1.44-1.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 134.3, 131.9, 129.9, 128.9, 125.4, 106.8, 61.8, 54.1, 49.8, 46.2, 32.6, 27.8; Mass Spectrum: M+H^+ 378.

Example 133

2-*tert*-Butyl-4-{[(5-methyl-3-phenylisoxazol-4-yl)methyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 1-(5-methyl-3-phenylisoxazol-4-yl)methanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.46 (m,

7H), 7.43-7.38 (m, 3H), 5.08 (t, 1H), 3.86 (d, 2H), 2.32 (s, 3H), 1.71 (s, 9).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 162.2, 159.2, 134.5, 131.4, 130.2, 130.1, 129.3, 128.9, 128.7, 128.1, 124.9, 109.6, 109.4, 61.9, 37.8, 27.8, 11.4; Mass Spectrum: M+H$^+$ 452.

Example 134

2-*tert*-Butyl-5-phenyl-4-{[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]amino}isothiazol-3(2H)-one 1,1-dioxide

Commercially available 1-(1,3,5-trimethyl-1H-pyrazol-4-yl)methanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61-7.56 (m, 2H), 7.49-7.43 (m, 3H), 4.96 (t, 1H), 3.68 (s, 5H), 2.11 (s, 3H), 2.07 (s, 3H), 1.73 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 146.3, 137.9, 134.9, 131.8, 129.8, 128.8, 125.4, 111.8, 107.8, 61.8, 38.8, 36.1, 27.8, 11.8, 9.8.; Mass Spectrum: M+H$^+$ 403.

Example 135

2-*tert*-Butyl-5-phenyl-4-[(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43-8.39 (m, 1H), 7.83-7.78 (m, 1H), 7.54-7.48 (m, 2H), 7.47-7.40 (m, 3H), 6.87-6.81 (m, 1H), 5.93 (brs, 1H), 4.37-4.32 (m, 2H), 3.29-3.23 (m, 2H), 1.73 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 159.7, 145.0, 145.0, 136.4, 136.3, 135.3, 131.7, 129.9, 129.0, 125.1, 123.0, 121.1, 120.8, 111.6, 108.0, 64.7, 61.8, 43.8, 27.8; Mass Spectrum: M+H$^+$ 470.

Example 136

2-*tert*-Butyl-5-phenyl-4-({2-[4-(trifluoromethoxy)phenyl]ethyl}amino)isothiazol-3(2H)-one 1,1-dioxide

2-[4-(Trifluoromethoxy)phenyl]ethanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.49-7.41 (m, 3H), 7.07-7.02 (m, 2H), 6.80-6.75 (m, 2H), 5.48-5.42 (m, 1H), 3.14-3.06 (m, 2H), 2.59-2.52 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 148.2, 136.4, 135.0, 131.9, 130.0, 130.0, 129.0, 125.3, 121.4, 107.6, 61.8, 45.0, 41.1, 35.4, 27.8; Mass Spectrum: M+H$^+$ 469.

Example 137

2-*tert*-Butyl-5-phenyl-4-[(2,2,2-trifluoroethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

Commercially available 2,2,2-trifluoroethanamine was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.45 (m, 5H), 5.42-5.36 (m, 1H), 3.52-3.45 (m, 2H), 1.73 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 133.8, 131.3, 130.5, 129.2, 124.5, 123.5, 122.3, 111.0, 61.9, 44.8, 44.5, 44.3, 44.0, 27.5; Mass Spectrum: $M+H^+$ 363.

Example 138

2-*tert*-Butyl-4-[(2,3-dihydroxypropyl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 3-aminopropane-1,2-diol was also used as starting material to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.45 (m, 2H), 7.45-7.40 (m, 3H), 5.75 (brs, 1H), 3.65-3.58 (m, 1H), 3.43-3.36 (m, 1H), 3.32-3.24 (m, 1H), 3.02-2.85 (m, 2H), 2.11 (brs, 2H), 1.72 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 135.5, 131.8, 130.0, 129.0, 125.1, 107.7, 70.2, 64.3, 61.9, 46.3, 27.8; Mass Spectrum: $M+H^+$ 355.

Example 139

3-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propanenitrile

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.42 (m, 5H), 5.63-5.56 (m, 1H), 3.22-3.13 (m, 2H), 2.25-2.17 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 134.5, 131.6, 130.6, 129.3, 124.4, 117.1, 109.4, 62.1, 39.5, 27.8, 18.5; Mass Spectrum: $M+H^+$ 334 Commercially available 3-aminopropanenitrile was also used as starting material to give the title compound.

Examples 140 to 143 were prepared from 2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl 4-methylbenzenesulfonate and the appropriate phenol or thiophenol in analogy with the descriptions for Example 99 and 101-103. The starting material is either commercially available or can be prepared as described in or in analogy with the methods in the section for synthesis of starting material and intermediates or can be prepared according to methods known to person skilled in the art.

Example 140

2-*tert*-Butyl-5-phenyl-4-[(2-{[3-(trifluoromethoxy)phenyl]thio}ethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

Commercially available 3-(trifluoromethoxy)benzenethiol was also used as starting material to give the title compound. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.73 (s, 9H), 2.84 (t, 2H), 3.10 (q, 2H), 5.59 (bs, 1H), 7.07-7.09 (m, 2H), 7.14 (d, 1H), 7.30 (t, 1H), 7.38-7.46 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$): δ 27.82, 33.62, 42.54, 61.86, 108.39, 119.41, 120.59 (q, J=258.1Hz), 122.37, 124.90, 128.26, 128.99, 130.05, 130.57, 131.53, 134.81, 136.94, 149.74, 159.59; Mass Spectrum: M+$NH4^+$ 517.7.

Example 141

2-*tert*-Butyl-4-{[2-(4-chlorophenoxy)ethyl]amino}-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 4-chlorophenol was also used as starting material to give the title compound. ^{1}H NMR (500MHz $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.50-7.42 (m, 3H), 7.24 (d, 2H), 6.76 (d, 2H), 5.62 (t, 1H), 3.84 (t, 2H), 3.28-3.22 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): 159.6, 156.9, 135.2, 131.7, 130.0, 129.7, 129.0, 126.7, 125.1, 115.9, 108.3, 66.3, 61.9, 43.4, 27.8; Mass Spectrum: M+H^+ 435.

Example 142

2-*tert*-Butyl-5-phenyl-4-({2-[3-(trifluoromethoxy)phenoxy]ethyl}amino)isothiazol-3(2H)-one 1,1-dioxide

Commercially available 3-(trifluoromethoxy)phenol was also used as starting material to give the title compound. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.75 (s, 9H), 3.27 (q, 2H), 3.87 (t, 2H), 5.63 (t, 1H), 6.70 (s, 1H), 6.77 (m, 1H), 6.86 (m, 1H), 7.28-7.31 (m, 1H), 7.46-7.48 (m, 3H), 7.53-7.55 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 27.84, 43.28, 61.88, 66.34, 107.90, 108.41, 113.03, 113.92, 120.64 (q, J=256.2Hz), 125.06, 129.06, 130.07, 130.61, 131.70, 135.14, 150.36, 159.29, 159.65; Mass Spectrum: M+$NH4^+$ 501.8.

Example 143

4-{[2-(Biphenyl-2-ylthio)ethyl]amino}-2-tert-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commerically available bisphenyl-2-thiol was also used as starting material to give the title compound. ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.72 (s, 9H), 2.56 (t, 2H), 2.87 (q, 2H), 5.39 (bs, 1H), 7.26-7.44 (m, 14H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.84, 33.78, 42.49, 61.67, 107.71,

125.02, 127.42, 127.78, 128.34, 128.88, 129.61, 129.84, 130.94, 131.25, 131.57, 132.58, 134.86, 140.70, 144.20, 159.46; Mass Spectrum: M+H$^+$ 492.9.

Examples 144 and 145 were prepared from 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) and the appropriate acyl halide in analogy with the descriptions for Example105, 111 and 112. The starting material is either commercially available or can be prepared as described in or in analogy with the methods in the section for synthesis of starting material and intermediates or can be prepared according to methods known to person skilled in the art.

Example 144

4-[(1-Acetylpiperidin-4-yl)amino]-2-tert-butyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available acetyl chloride was also used as starting material to give the title compound. ^{1}H NMR (500MHz $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.49-7.43 (m, 3H), 5.20 (d, 1H), 4.39-4.33 (d, 1H), 3.63-3.57 (m, 1H), 3.16-3.08 (m, 1H), 2.58 (ddd, 1H), 2.24 (ddd, 1H), 1.86-1.64 (m, 11H), 1.28-1.19 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 169.0, 159.7, 133.9,131.9, 130.2, 128.9, 125.2, 107.6, 61.9, 50.3, 44.8, 40.1, 32.9, 32.1, 27.8, 21.6; Mass Spectrum: M-H$^+$ 404

Example 145

2-*tert*-Butyl-4-[(1-isobutyrylpiperidin-4-yl)amino]-5-phenylisothiazol-3(2H)-one 1,1-dioxide

Commercially available 2-methylpropanoyl chloride was also used as starting material to give the title compound. ^{1}H NMR (500MHz $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.44-7.40 (m, 3H), 5.18 (d, 1H), 4.42-4.27 (m, 2H), 3.79-3.74 (m, 1H), 3.19-3.09 (m, 1H), 2.69 (sp, 1h), 2.62-2.52 (m, 1H), 2.30-2.20 (m, 1H), 1.78-1.66 (m, 11H), 1.29-1.17 (m, 2H), 1.12-1.02 (m, 6H); ^{13}C NMR (125MHz $CDCl_3$): 175.5, 159.8, 133.9, 131.8, 130.2, 128.9, 125.3, 107.5, 61.9, 50.4, 43.7, 40.3, 33.2, 32.2, 30.2, 27.8, 19.7, 19.5; Mass Spectrum: M-H$^+$ 432.

Example 146

2-*tert*-Butyl-5-phenyl-4-{[1-(2-phenylethyl)piperidin-4-yl]amino}isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75) and (2-bromoethyl)benzene in a similar manner as described for Example104. ^{1}H NMR (500MHz $CDCl_3$): δ 7.64-7.50 (m, 2H), 7.48-7.45 (m, 3H), 7.30-7.25 (m, 2H), 7.22-7.17 (m, 1H), 7.16-7.12 (m, 2H), 5.22 (d, 1H), 3.00-2.90 (m, 1H), 2.81-2.74 (m, 2H), 2.73-2.67 (m, 2H), 2.50-2.43 (m, 2H), 1.82-1.60 (m, 13H), 1.46-1.36 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 140.2, 134.3, 131.9, 130.0, 128.9, 128.6, 126.3, 125.4, 106.9, 61.8, 60.2, 51.8, 50.2, 33.8, 32.4, 27.9; Mass Spectrum: M+H$^+$ 468

Example 147

2-*tert*-Butyl-5-phenyl-4-{[2-(pyrrolidin-3-ylthio)ethyl]amino}isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from Example 100 in analogy with the description of 2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide (Example 75). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.68-1.75 (m, 10H), 1.98 (s, 4H), 2.12-2.19 (m, 1H), 2.49 (t, 2H), 2.83-2.86 (m, 1H), 3.06-3.14 (m, 4H), 3.20-3.25 (m, 1H), 3.31-3.35 (m, 1H), 5.71 (t, 1H), 7.44-7.46 (m, 3H), 7.50-7.52 (m, 2H), 8.02 (bs, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 23.12, 27.82, 31.51, 32.59, 41.96, 43.05, 44.42, 51.25, 61.87, 108.12, 125.11, 129.06, 130.08, 131.65, 134.85, 159.64; Mass Spectrum: M+H$^+$ 410.1.

Example 148

2-*tert*-Butyl-4-{[(5-methylisoxazol-3-yl)methyl]-amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

The title compound was prepared as described for Example 24 from 1 equivalent of [(5-methylisoxazol-3-yl)methyl]-amine, 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1 equivalent TEA with a reaction time of 45mins. The mixture was evaporated and purified by silica gel column chromatography (Horizons Biotage) using 35% EtOAc in pentane as eluent to give the title compound (0.070g, 56%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.46-7.41 (m, 3H), 5.73 (s, 1H), 5.66 (t, 1H), 5.07 (d, 2H), 2.39 (s, 3H), 1.74 (s, 9H); ^{13}C NMR (125MHz CDCl3): δ 170.7, 159.9, 159.4, 134.8, 131.6, 130.1, 128.9, 124.7, 109.3, 100.4, 61.9, 40.4, 27.8, 12.5; Mass Spectrum: M+H$^+$ 376

Example 149

4-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and [2-(3,4-dimethoxyphenyl)ethyl]amine in a similar manner as described for Example 24. ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.52 (m, 2H), 7.50-7.46 (m, 3H), 6.76 (d, 1H), 6.46 (dd, 1H), 6.36 (d, 1H), 5.40 (t, 1H), 4.41 (sept, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.13 (q, 2H), 2.57 (t, 2H), 1.59 (d, 6H); ^{13}C NMR (125MHz, CDCl3): δ 158.7, 149.3, 148.1, 135.4, 131.7, 130.0, 129.9, 128.8, 125.4, 120.8, 111.8, 111.7, 107.2, 56.1, 47.8, 45.3, 35.6, 20.3; Mass Spectrum M+H$^+$ 431

Example 150

4-{[2-(3-Chloro-4-methoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 2-*tert*-Butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and [2-(3-chloro-4-methoxyphenyl)ethyl]amine in a similar manner as described for Example 24. ^{1}H NMR (500MHz DMSO-d_6): δ 7.55-7.47 (m, 5H), 7.34 (t, 1H), 6.94 (d, 1H), 6.65 (dd, 1H), 6.61 (d, 1H), 4.32 (qt, 1H), 3.78 (s, 3H), 3.03-2.96 (m, 2H), 2.43-2.37 (m, 2H), 1.46 (d, 6H); ^{13}C NMR (125MHz DMSO-d_6): δ 158.7, 153.7, 136.1, 132.4, 131.9, 130.3, 129.4, 128.8, 126.1, 121.3, 113.3, 105.0, 56.7, 47.3, 45.0, 34.4, 20.5; Mass spectrum M+H$^+$ 435

Example 151

4-{2-[(2-Isobutyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

A mixture of 4-{2-[1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate (0.096g, 0.227mmol), 1-bromo-2-methylpropane (0.050g, 0.364mmol)) and TEA (0.041ml, 0.295mmol) in DMSO was heated in a microwave at 100°C for 40mins and at 130°C for 1h. The reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (Horizons Biotage) using 15-100% EtOAc in pentane as eluent to give the title compound (0.047g, 43%) as a solid; ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.46 (m, 5H), 7.15 (d, 2H), 6.84 (d, 2H), 5.43 (t, 1H), 3.52 (d, 2H), 3.21-3.15 (m, 2H), 3.14 (s, 3H), 2.64-2.58 (m, 2H), 2.32-2.23 (m, 1H), 1.02 (d, 6H); ^{13}C

NMR (125MHz $CDCl_3$): δ 159.6, 148.2, 136.9, 135.2, 131.8, 130.3, 130.2, 129.1, 125.2, 122.5, 107.8, 47.9, 44.9, 37.6, 35.5, 27.8, 20.3; Mass Spectrum: $M+H^+$ 479

Example 152

2-Isopropyl-5-phenyl-4-[(1-pyridin-2-ylpiperidin-4-yl)amino]isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-Chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-pyridin-2-ylpiperidine-4-amine dihydrochloride in a similar manner as described for Example 24 with TEA as base. ^1H NMR (500MHz $CDCl_3$): δ 8.14 (dd, 1H), 7.58-7.53 (m, 2H), 7.48-7.41 (m, 4H), 6.62-6.55 (m, 2H), 5.23 (d, 1H), 4.42 (sept, 1H), 4.10-4.02 (m, 2H), 3.22-3.12 (m, 1H), 2.49-2.41 (m, 2H), 1.80-1.72 (m, 2H), 1.59 (d, 6H), 1.42-1.33 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): 159.2, 158.7, 148.1, 137.7, 134.5, 131.9, 130.2, 128.9, 125.3, 113.6, 107.5, 106.9, 50.8, 47.8, 44.1, 32.1, 20.4; Mass Spectrum: M+H+ 427

Example 153

4-(2-{[2-(4-Fluorobenzyl)-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl]amino}ethyl)phenyl methanesulfonate

The title compound was prepared from 4-{2-[1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate and 1-(bromomethyl)-4-fluorobenzene in a similar manner as described for Example 151. ^1H NMR (500MHz $CDCl_3$): δ 7.56-7.46 (m, 7H), 7.14 (d, 2H), 7.06 (t, 2H), 6.83 (d, 2H), 5.39 (t, 1H), 4.80 (s, 2H), 3.19-3.14 (m, 2H), 3.13 (s, 3H), 2.61 (t, 2h); ^{13}C NMR (125MHz $CDCl_3$): 163.9, 161.9, 159.0, 148.2, 136.8, 135.2, 131.8, 131.1, 131.0, 130.3, 129.2, 124.9, 122.5, 115.9, 115.7, 107.9, 44.9, 43.1, 37.7, 35.5; Mass Spectrum: $M+H^+$ 531

Example 154

2-Isopropyl-4-(isopropylamino)-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and isopropylamine in a similar manner as described for Example 24. ^1H NMR (500MHz $CDCl_3$): δ 7.56-7.51 (m, 2H), 7.48-7.43 (m, 3H), 5.14 (d, 1H), 4.42 (sept, 1H), 3.40-3.30 (m, 1H), 1.60 (d, 6H), 1.00 (d, 6H); ^{13}C NMR (125MHz $CDCl_3$): δ 158.9, 134.6, 131.7, 129.9, 128.9, 125.5, 106.3, 47.8, 44.9, 23.0, 20.4; Mass Spectrum: M+H+ 309.

Example 155

2-Isopropyl-5-phenyl-4-[(1-pyridin-2-ylazetidin-3-yl)amino]isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-pyridine-2-ylazetidin-3-amine in a similar manner as described for Example 118. ^{1}H NMR (500MHz $CDCl_3$): δ 1.57 (d, 6H), 3.71-3.75 (m, 2H), 3.84 (t, 2H), 4.04-4.10 (m, 1H), 4.37-4.45 (m, 1H), 5.71-5.76 (m, 1H), 6.19 (d, 1H), 6.60-6.64 (m, 1H), 7.40-7.44 (m, 1H), 7.46-7.52 (m, 5H), 8.10-8.12 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 20.36, 44.88, 48.00, 58.15, 106.25, 109.08, 113.90, 124.58, 129.24, 130.35, 131.46, 134.60, 137.46, 148.39, 158.35, 160.10; Mass Spectrum: $M+H^+$ 399.

Example 156

4-{[2-(4-Hydroxy-3,5-dimethoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-(2-aminoethyl)-2,6-dimethoxyphenol in a similar manner as described for Example 118. ^{1}H NMR (THF-d_8, 500MHz): δ 1.53 (d, 6H), 2.45 (t, 2H), 3.11 (q, 2H), 3.73 (s, 6H), 4.31-4.39 (m, 1H), 6.03 (s, 2H), 6.47 (t, 1H), 7.22 (s, 1H), 7.46-7.50 (m, 3H), 7.55-7.57 (m, 2H); ^{13}C NMR (125MHz, THF-d8): δ 19.57, 35.92, 45.47, 46.98, 55.93, 106.13, 106.56, 126.64, 127.87, 128.56, 129.34, 131.86, 135.49, 135.64, 148.12, 158.61; Mass Spectrum: $M+H^+$ 447.

Example 157

4-{[2-(2-Aminopyridin-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared in two steps. *tert*-Butyl (4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}pyridin-2-yl)carbamate was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and *tert*-butyl [4-(2-aminoethyl)pyridin-2-yl]carbamate in a similar manner as described for Example 118. Deprotection of *tert*-butyl (4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}pyridin-2-yl)carbamate in a similar manner as described for 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-amine gave the title compound.

Example 158

2-Isopropyl-5-phenyl-4-[(2-pyridin-4-ylethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and (2-pyridin-4-ylethyl)amine in a similar manner as described for Example 118. ^{1}H NMR (500MHz $CDCl_3$): δ 1.59 (d, 6H), 2.58 (t, 2H), 3.18 (q, 2H), 4.37-4.45 (m, 1H), 5.44 (t, 1H), 6.71-6.73 (m, 2H), 7.46-7.57 (m, 5H), 8.44-8.46 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 20.37, 35.42, 44.14, 47.90, 107.90, 123.96, 125.15, 129.14, 130.19, 131.83, 135.12, 146.48, 150.27, 158.57; Mass Spectrum: $M+H^+$ 372.

Example 159

2-Isopropyl-5-phenyl-4-[(2-pyridin-3-ylethyl)amino]isothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and (2-pyridin-3-ylethyl)amine in a similar manner as described for Example 118. ^{1}H NMR (500MHz $CDCl_3$): δ 1.59 (d, 6H), 2.59 (t, 2H), 3.17 (q, 2H), 4.37-4.45 (m, 1H), 5.47 (t, 1H), 7.06-7.09 (m, 1H), 7.14-7.17 (m, 1H), 7.46-7.55 (m, 5H), 8.07 (s, 1H), 8.44-8.46 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 20.38, 33.39, 44.78, 47.88, 107.76, 123.70, 125.15, 129.13, 130.20, 131.84, 133.02, 135.16, 136.13, 148.57, 150.06, 158.61; Mass Spectrum: $M+H^+$ 372.

Example 160

4-[2-({2-[(Methylthio)methyl]-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl}amino)ethyl]phenyl methanesulfonate

The title compound was prepared from 4-{2-[1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate and 1,1,1-trifluoro-2-iodoethane in a similar manner as described for Example 151; ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.48 (m, 5H), 7.16 (d, 1H), 6.85 (d, 2H), 5.41 (t, 1H), 4.77 (s, 2H), 3.21-3.15 (m, 1H), 3.14 (s, 3H), 2.63 (t, 2H), 2.38 (s, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.1, 148.2, 136.8, 135.2, 131.8, 130.4, 130.3, 129.2, 124.8, 122.5, 108.2, 45.0, 44.5, 37.7, 35.5, 16.8; Mass Spectrum: M+H+ 483.

Example 161

4-{[2-(3,5-Dimethylisoxazol-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and [2-(3,5-dimethylisoxazol-4-yl)ethyl]amine in a similar manner as described for Example 24. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.49-7.45 (m, 3H), 5.32 (t, 1H), 4.47 (sept, 1H), 3.04 (q, 2H), 2.33 (t, 2H), 2.14 (s, 3H), 2.01 (s, 3H), 1.59 (d, 6H); ^{13}C NMR (125MHz, $CDCl_3$): δ 166.1, 159.4, 158.6, 134.9, 131.4, 130.2, 129.2, 125.1, 109.7, 107.9, 47.9, 43.3, 23.0, 20.4, 11.1, 10.2; Mass Spectrum: M+H+ 390

Example 162

4-{[2-(3,5-Dimethyl-1H-pyrazol-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

The title compound was prepared from 4-chloro-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and [2-(3,5-dimethyl-1*H*-pyrazol-4-yl)ethyl]amine dihydrochloride in a similar manner as described for Example 24 with TEA as base. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.53-7.48 (m, 2H), 7.47-7.43 (m, 3H), 5.34 (t, 1H), 4.41 (sept, 1H), 3.01 (q, 2H), 2.41 (t, 2H), 2.05 (s, 6H), 1.58 (d, 6H); ^{13}C NMR (125MHz $CDCl_3$): δ 158.8, 135.3, 131.5, 129.9, 129.0, 125.3, 111.2, 107.2, 47.8, 43.9, 23.7, 20.4, 10.9; Mass Spectrum: M+H+ 389

Example 163

4-[2-({2-[(5-Methylisoxazol-3-yl)methyl]-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl}amino)ethyl]phenyl methanesulfonate

The title compound was prepared from 4-{2-[1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate and 3-(bromomethyl)-5-methylisoxaole in a similar manner as described for Example 151; ^{1}H NMR (500MHz $CDCl_3$): δ 7.57-7.46 (m, 5H), 7.13 (d, 2H), 6.82 (d, 2H), 6.16 (s, 1H), 5.43 (t, 1H), 4.87 (s, 2H), 3.22-3.08 (m, 5H), 2.61 (t, 3H), 2.41 (s, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 170.8, 158.9, 158.6, 148.2, 136.8, 135.2, 131.8, 130.4, 130.3, 129.2, 124.7, 122.5, 108.1, 101.8, 45.0, 37.7, 35.5, 35.1; Mass Spectrum: $M+H^+$ 518

Example 164

2,6-Dimethylphenyl 4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]butanoate

2,6-Dimethylphenyl 4-aminobutanoate hydrochloride (80.4 mg, 0.33 mmol) and 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide (89.9 mg, 0.91 mmol) were dissolved in a

mixture of MeCN/DMF (4:1, 5 ml, dry). TEA (0.134 ml) was added and the reaction mixture was stirred at rt for 15 h. Diethyl ether (30 ml) was added and the resulting mixture was extracted with water (2x 10 ml). The organic layer was dried ($MgSO_4$), evaporated and the residue was purified by column chromatography on silica, using n-heptane/EtOAc (7:3) as eluent. The obtained product was further purified by re-chromatography, using the same conditions as before, to give the title compound (17 mg, 11%) as colorless oil, which solidified upon standing. ^1H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 9H), 1.78-1.85 (m, 2H), 2.06 (s, 6H), 2.38 (t, 2H), 2.96-3.01 (m, 2H), 5.37 (bt, 1H), 7.04 (s, 3H), 7.42-7.44 (m, 3H), 7.50-7.52 (m, 2H).

Example 165

2-Mesitylethyl N-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

The title compound was prepared from [(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetic acid and methyl glycinate hydrochloride. Mass Spectrum: $[M+H]^+$ 485.21, $[M-H]^-$ 483.28.

Example 166

2-[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl (2,6-dimethylphenyl)acetate

The title compound was prepared from Example 76 and (2,6-dimethylphenyl)acetic acid. Mass Spectrum: $[M+H]^+$ 471.21, $[M-H]^-$ 469.34.

Example 167

Phenyl N-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

The title compound was prepared from 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and phenyl β-alaninate hydrochloride in a similar manner as described for Example 164. Mass Spectrum: $[M+H]^+$ 429.11, $[M-H]^-$ 427.14.

Example 168

4-(Trifluoromethoxy)phenyl N-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

The title compound was prepared from 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 4-(trifluoromethoxy)phenyl β-alaninate in a similar manner as described for Example 164. Mass Spectrum: $[M+H]^+$ 513.12, $[M-H]^-$ 511.16.

Example 169

1-Methylpiperidin-4-yl N-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

The title compound was prepared from 2-*tert*-butyl-4-chloro-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide and 1-methylpiperidin-4-yl β-alaninate hydrochloride in a similar manner as described for Example 164. Mass Spectrum: $[M+H]^+$ 450.12, $[M-H]^-$ 448.23.

Example 170

2-Mesityl-1-methylethyl [(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-Dihydroisothiazol-4-yl)amino]acetate

The title compound was prepared from [(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetic acid and 1-mesitylpropan-2-ol. Mass Spectrum: $[M+H]^+$ 499.15, $[M-H]^-$ 497.98.

Example 171

4-Methoxybenzyl N-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

[(2-*tert*-Butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetic acid (100mg, 0.30mmol), (4-methoxyphenyl)methanol (204mg, 1.48mmol), TEA (123μL) and DMAP (9mg, 0.074mmol) were dissolved in DCM (10mL). DMF 81mL) and EDC (113mg, 0.59mmol) was added and the solution was stirred at 40°C over night. Aqueous K_2CO_3 (1M, 50mL) was added and the reaction mixture was extracted with DCM. The organic phases were combined, dried over $MgSO_4$, filtered and evaporated. The residue was purified by preparative HPLC affording the title compound (23mg, 17%). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.69 (s, 9H), 3.54 (s, 2H), 3.77 (s, 3H), 4.98 (s, 2H), 5.79 (t, 1H), 6.83 (d, 2H), 7.17 (d, 2H), 7.32-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7, 45.4, 55.5, 61.8, 67.6, 109.6, 114.2, 124.4, 127.0, 128.9, 130.1, 130.7, 131.5, 134.8, 159.2, 160.2, 168.7.

Example 172

4-Methoxyphenyl N-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

The title comound was prepared from [(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetic acid and 4-methoxyphenol as described for Example 171 affording the title compound (28mg, 21%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 9H), 3.77 (s, 3H), 3.81 (d, 2H), 5.78 (t, 1H), 6.85 (dd, 4H), 7.44-7.51 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8, 45.6, 55.8, 61.9, 110.1, 114.7, 122.0, 124.5, 129.1, 130.2, 131.6, 134.8, 143.6, 157.8, 159.2, 167.8.

Biological activity

Co-Activator recruitment assay

The Ligand Binding Domain (LBD) of human LXRalpha (amino acid 205-447) and LXRbeta (amino acid 216-461) was produced by recombinant techniques in E coli. A fragment of the human Steroid Receptor Co-Activator-1 (SRC-1) was produced as a synthetic peptide. An anti-6xHis-antibody coupled with Europium (Eu^{3+}) was used to recognize the His-tag on the LXR-LBD and Allophycocyanin (APC) coupled to streptavidin was used to recognize the biotinylated SRC-1. Agonist binding to LXRalpha or LXRbeta enhances the affinity of LXR towards SRC-1 and thereby brings Eu^{3+} and APC in close proximity. Eu^{3+} is excited at 337 nm and emitts light at 620 nm. This emission, when in close proximity, excites APC to emit light at 665 nm.

Compounds (10mM) in DMSO were diluted (1/3) in DMSO in 10 concentrations. This dilution plates were further diluted in buffer {20mM [Tris(hydroxymethyl)aminomethane] pH 7.5, 0.125% CHAPS {3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate}, 2mM DTT (Dithiothreitol) and 0.05% BSA (Bovine Serum Albumin)} in order to reduce DMSO concentration, 0.5 μl to 13.5 μl. To this, 6 μl assay mix was added, giving an maximal assay concentration of 83 μM, and the plates (384-well V-groove plates) were incubated at room temperature for 60 to 80 min.. The assay mix has the following final concentrations; LXRalpha mix: 0.06 μg/mL Eu-labelled anti-6x His Ab, 1.15μg/mL Streptavidin APC, 30 nM SRC-1 peptide and 0.9 μg/mL LXRalpha in buffer and LXRbeta mix; 0.06 μg/mL Eu-labelled anti-6x His Ab, 1.15μg/mL Streptavidin APC, 90 nM SRC-1 peptide and 0.2 μg/mL LXRbeta in buffer. Time-resolved fluorescence readings were done in a Wallac Victor reader at 665 nm followed by reading at

615 nm. The LXR ligand, 22-R Hydroxycholesterol or an internal compound at 50μM was used as the 100% control.

Transactivation assay

Expression vectors were prepared by inserting the ligand binding domain cDNA (complementary DNA) of human LXRalpha (amino acid 205-447) and LXRbeta (amino acid 216-461) in frame with, 3´ to the yeast GAL4 transcription factor DNA binding domain and the nuclear localization signal from the T-antigen of Polyoma Virus in the eucaryotic expression vector pSG5 (Stratagene). The resulting expression vectors pSGGAL-LXRalpha and pSGGAL-LXRbeta were used in cotransfection experiments together with the pGL3 luciferase reporter plasmid containing a minimal SV40 promoter (Promega) and five copies of the UAS GAL4 recognition site. 2.5 μg pSGGAL-LXRalpha or beta were mixed with 25 μg pGL3 5xUAS and 22.5 μg pBluscript (Stratagene) in 0.95 mL ice cold PBS containing approx. 4-9 milj. U2/OS osteosarcoma cells. After a five minute incubation on ice the cell/DNA mixture was electroporated in 0.4 cm cuvettes at 960 μF, 230 V using a BioRad electroporator and diluted to 0.32 milj cells /mL in complete DMEM [Dulbecco's Modified Eagle Medium w/o phenol red, (Gibco 11880-028) including 10% FBS (Foetal Bovine Serum), 1% PEST (Penicillin Streptomycin), 20mM Hepes, 2mM L-Glutamine and 0.36% Glucose Gibco 31966-021] medium. Cells from at least two electroporations were pooled in order to avoid variations between different electroportations. 25 μl diluted, electroporated cells, were seeded into 384-well plates (0.8 x 10^4 cells/well) and the cells were allowed to adhere for 2 h at 37°C, 5% CO_2 in a cell culture incubator. Compounds (10mM) in DMSO were diluted (1/3) in DMSO in 10 concentrations. This dilution plates were further diluted in complete DMEM w/o phenol red (2.5μl to 97.5μl) in order to reduce DMSO concentration. 7 μl of this was added to the electroporated cells in 384-well plates and incubation was continued for 48 h in a cell culture incubator, after which cells were lysed by adding 32 μl/well LucLite luciferase substrate. Luciferase activity was measured as Luminescence in the Wallac Victor reader after 15 min. incubation at room temperature. The LXR ligand, Tularik T0901317, or an internal standard, at 1μM was used as the 100% control.

In vivo assay

Separation of the desired antiatherogenic and the undesired lipogenic effects of LXR ligands was tested in normal C57 BL6 mice where the test agents are administered for three

days (4 doses) in different or fixed oral doses. Gavage was performed once daily about noon, except the last dose that was given at 0700 hours, 3 hours before anaesthesia. 30 Mice were used in each screen and these were divided into five groups with six animals in each. One group was control group and the remaining 4 groups were treated with test agents in fixed or different doses. The test agents were given by gavage once daily for three days in four doses totally.

Blood samples were then obtained under anaesthesia for determination of plasma levels of TG. The liver was removed for determination of liver weight and TG content. 20-50mg tissue, liver or intestine (first 2-3 cm distal the stomach) was snap-frozen in liquid nitrogen at necropsy for later analysis of any up regulation of LXR target genes, primarily ABCA1, ABCG1, SREBP1c and FAS. The tissues are kept in a –80°C freezer until analysis.

Stainless steel beads (Cat. No. 69989, QIAGEN) were added to collection micro tubes, one bead per tube, (Cat. No.19560, QIAGEN), while the tubes were kept on dry ice. Tissues were transferred to the collection micro tubes after which 750µl QIAzol (Cat. No.79306, QIAGEN) was added and then the tubes were placed in a Mixer Mill and homogenized for 2 x 5 minutes at 25 Hz. After homogenization the 96-well plate was centrifuged at 6000 x g for one minute at 4°C in a Sigma 4K-15C centrifuge. 150µl chloroform was added to all samples, which were shaken vigorously for 15 seconds and incubated at room temperature for 2-3 minutes and centrifuged again at 6000 x g for 15 minutes. 200µl of the upper aqueous phase was transferred to Square-well tubes (Cat. No.19573, QIAGEN) and one volume of 70% ethanol was added and mixed by pipetting up and down. After a 10 minute incubation on ice 250µl samples was loaded onto the wells of a 96-well culture cluster plate (Cat. No. 3595, Corning Incorporated)

RNA was purified using an ABI Prism 6700 or ABI Prism 6100 according to the manufacturers recommendations. RNA was eluted in 150µl with a concentration of 50-200ng/µl and 10µl of this was analyzed by agarose gel electrophoresis (non denaturating 1% TBE gel) to verify RNA quality. cDNA synthesis was performed using the High-Capacity Archive Kit (Cat. No 4322171, Applied Biosystems) according to the manufacturers recommendations, by random primers, in a total reaction volume of 50µl/sample.

Gene expression mRNA levels were determined by real-time PCR (7500 Real-time PCR system, Applied Biosystems). Taqman universal PCR master mix (Cat.No. 4305719, Applied Biosystems) was used in a 25µl reaction containing 400nM of each target primer, 100nM of each of the control primers (36B4), 200nM of the target probe, 100nM of the

control probe (36B4) and 2.5–10ng of sample cDNA. The threshold cycles (Ct) for the endogenous control gene 36B4 and target genes were determined and relative mRNA levels were calculated using the comparative Ct method and expressed as fold induction.

The following primer and probes were used: ABCA1 Forward; 5´-AAGGGTTTCTTTGCTCAGATTGTC-3´, ABCA1 Reverse; 5´-TGCCAAAGGGTGGCACA-3´, ABCA1 Probe; 5´-FAM-CCAGCTGTCTTTGTTTGCATTGCCC –TAMRA-3´, ABCG1 Forward; 5´-CCATGAATGCCAGCAGCTACT-3´, ABCG1 Reverse; 5´-CACTGACACGCACACGGACT-3´, ABCG1 Probe; 5´-FAM-TGCCGCAATGACGGAGCCC–TAMRA-3´, FAS Forward; 5´-GGCATCATTGGGCACTCCTT-3´, FAS Reverse; 5´-GCTGCAAGCACAGCCTCTCT-3´, FAS Probe; 5´-FAM-CCATCTGCATAGCCACAGGCAACCTC-TAMRA-3´, SREBP1c Forward; 5´-GGAGCCATGGATTGCACATT-3´, SREBP1c Reverse; 5´-CCTGTCTCACCCCCAGCATA-3´, SREBP1c Probe; 5´-FAM-CAGCTCATCAACAACCAAGACAGTGACTTCC-TAMRA-3´, 36B4 Forward; 5´-GAGGAATCAGATGAGGATATGGGA-3´, 36B4 Reverse; 5´-AAGCAGGCTGACTTGGTTGC-3´, 36B4 Probe; 5´-VIC-TCGGTCTCTCGACTAATCCCGCCAA–TAMRA-3´.

From dose-response relationships, selectivity values (relative potencies) were determined to discriminate between the primary intestinal up regulation of LXR target genes and the unwanted plasma and hepatic TG elevations, respectively.

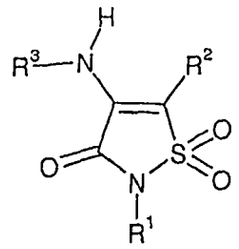
The compounds of formula I have an EC_{50} of less than 50 μmol/l for LXRα and/or β in coactivator recruitment assays and/or reporter gene assays. For example, the compounds of Example 6 and Example 10 have EC_{50}'s for LXRα of 0.58 μmol/l and 1.42 μmol/l in the coactivator recruitment assay, respectively, and the compounds of Examples 2 and Example 7 have EC_{50}'s for LXRα of 1.36 μmol/l and 0.27 μmol/l in reporter gene assay.

In addition the compounds of the present invention exhibit favourable pharmacological effects *in vivo*.

The compounds of the present invention also have a promising toxicological profile

CLAIMS

1. A compound of general formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof,

wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

or R^1 is cycloalkyl or heterocyclyl each optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is phenyl or heteroaryl each optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^1 is phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

R^2 represents

phenyl which is optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$,$S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$;

or R^3 is MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$ $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b,

SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$,$S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

and in the above definitions

X represents a straight or branched, saturated or unsaturated alkyl group having 1 to 6 carbon atoms wherein said alkyl group may optionally be interrupted by O, S, SiR^bR^b, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2;

Y which binds to the nitrogen in the 2-position of the isothiazol-3(2*H*)-one 1,1-dioxide and represents a straight or branched, saturated or unsaturated alkylene group having 1 to 3 carbon atoms wherein said alkyl group may optionally be interrupted or ended by one of the following: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c and/or Y is optionally substituted by one or more of the following independently selected from: OH, F, CN, NR^aR^a, C_1-C_4alkyl, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$ or SO_2R^b;

Z binds to E or Het^4 and one of the following: Q, Het^1, R or Het^2, and represents a straight or branched, saturated or unsaturated alkylene group having 1 to 6 carbon atoms wherein said alkylene group may optionally be interrupted or ended by one of the following: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, or is one of the following: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2 and/or Z is optionally substituted by one or more of the following independently selected from: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $SiR^bR^bR^b$, $S(O)R^c$, SO_2R^c, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is optionally substituted by one or more of the following: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, OR^b;

M represents a saturated or unsaturated non-aromatic monocarbocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring system composed of 8, 9 or 10 carbon atoms;

E represents a saturated or unsaturated non-aromatic monocarbocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated non-aromatic or partly aromatic bicyclic ring system composed of 8, 9 or 10 carbon atoms, and the ring binds, unless otherwise specified, through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide;

A represents an aromatic monocyclic ring composed of 6 carbon atoms or an aromatic bicyclic ring system composed of 10 carbon atoms;

P binds to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide and represents a straight or branched, saturated or unsaturated alkylene group having 1 to 6 carbon atoms wherein the alkylene group is optionally interrupted or ended by one of the following: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 and/or P is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, phenyl, phenylC_1-C_3alkyl, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or OR^b;

Q represents a saturated or unsaturated non-aromatic monocyclic ring composed of 3, 4, 5, 6, 7 or 8 carbon atoms, which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a,

OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

R represents a phenyl group which is optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

T binds to M, Het^3, A or Het^5 and one of the following: Q, Het^1, R or Het^2; and represents methylene or is one of the following: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a or NR^aSO_2;

Het^1 represents a saturated or unsaturated non-aromatic 3, 4, 5, 6, 7, 8, 9 or 10 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur, and wherein the ring optionally is substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

Het^2 represents an aromatic 5 or 6 membered monocyclic ring in which one or more of the atoms in the ring is an element other than carbon independently selected from one or more of for example nitrogen, oxygen and sulfur, and which is substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, phenylC_1alkyl, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$or $NR^aC(O)NR^aR^a$;

Het^3 represents a saturated or unsaturated non-aromatic 3, 4, 5, 6, 7, 8, 9 or 10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 9 or 10 membered bicyclic ring system in which one or more of the atoms in the monocyclic ring or bicyclic ring system is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur;

Het^4 represents a saturated or unsaturated non-aromatic 3, 4, 5, 6, 7, 8, 9 or 10 membered monocyclic ring or a saturated or unsaturated non-aromatic or partly aromatic 9 or 10 membered bicyclic ring system in which one or more of the atoms in the monocyclic ring or bicyclic ring system is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur, and the ring binds, unless otherwise specified, through its non-aromatic part to nitrogen in 4-position on the isothiazol-3(2*H*)-one 1,1-dioxide;

Het^5 represents an aromatic 5 or 6 membered monocyclic ring or an aromatic 9 or 10 membered bicyclic ring system in which one or more of the atoms in the monocyclic ring or bicyclic ring system is an element other than carbon independently selected from one or more of for example nitrogen, oxygen or sulfur;

R^a independently represents H or a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F;

R^b independently represents a straight or branched, saturated or unsaturated C_1-C_4alkyl chain optionally substituted by one or more F; and

R^c independently represents H or a straight or branched, saturated or unsaturated C_1-C_3alkyl chain optionally substituted by one or more F.

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

or R^1 is cycloalkyl or heterocyclyl each optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b,

$SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or $C(O)R^b$;

or R^1 is phenyl or heteroaryl each optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

or R^1 is cycloalkylY or heterocyclylY wherein cycloalkyl or heterocyclyl each optionally is substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

or R^1 is phenylY or heteroarylY wherein phenyl or heteroaryl each optionally is substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 represents

phenyl which is optionally substituted by one or more of the following independently selected from: halogen (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

3. A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$,

$NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

4. A compound according to claim 3 or a pharmaceutically acceptable salt thereof wherein

R^1 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b or $C(O)R^b$.

5. A compound according to claim 1 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

6. A compound according to claim 1 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-

C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

7. A compound according to claim 1 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which

is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the folowing independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

8. A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

9. A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$,

$NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is

AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

10. A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$,

$NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

11. A compound according to claim 3 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

12. A compound according to claim 3 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

13. A compound according to claim 3 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$,

$C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and E or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

14. A compound according to claim 4 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

X which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ or $NR^aC(O)NR^aR^a$.

15. A compound according to claim 4 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

MP or Het^3P wherein M and Het^3 each optionally is substituted on the non-aromatic ring by one or more of the following independently selected from: F,

OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and wherein M or Het^3 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$;

or R^3 is AP or Het^5P wherein A and Het^5 each optionally is substituted by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

16. A compound according to claim 4 or a pharmaceutically acceptable salt thereof wherein

R^3 represents

E or Het^4 each optionally substituted on the non-aromatic ring by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b,

$SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$,

and Ė or Het^4 each optionally is substituted on the aromatic ring by one or more of the following independently selected from: halogen (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, or C_1-C_4alkyl which is optionally substituted by one or more of the following independently selected from: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ or $NR^aC(O)NR^aR^a$.

17. A compound according to claim 1 in which R^1 is selected from ethyl, isopropyl, n-butyl, *tert*butyl, cyclopentyl, hexyl, benzyl, 2-methoxyethyl, pyridin-2ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, tetrahydrofuran-2-ylmethyl, 2-(3-fluorophenyl)ethyl, isobutyl, 4-fluorobenzyl, (5-methylisoxazol-3-yl)methyl or (methylthio)methyl;

R^2 is phenyl; and

R^3 is selected from n-butyl, n-hexyl, benzyl, 3-[3-(hydroxymethyl)phenoxy]propyl, 4-phenylbutyl, 3-(2-methoxyphenoxy)propyl, 3-[4-(hydroxymethyl)phenoxy]propyl, 3-(2-fluorophenoxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(pyridin-3-yloxy)propyl, 3-(pyridin-4-yloxy)propyl, 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 3-(phenylthio)propyl, 3-phenoxypropyl, 3-(3-chlorophenoxy)propyl, 3-(3-fluorophenoxy)propyl, 3-(4-fluorophenoxy)propyl, 1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl, *cis*-4-hydroxycyclohexyl, 4-phenoxybutyl, 3-[(1-oxidopyridin-3-yl)oxy]propyl, 3-(4-methoxyphenoxy)propyl, 4,4-difluorocyclohexyl, 2-phenoxyethyl, 2-phenylethyl, 4-(difluoromethoxy)benzyl, *trans*-4-hydroxycyclohexyl, 3-hydroxypropyl, 2,3-dihydro-1,4-benzodioxin-2-ylmethyl, 4-hydroxycyclohexyl, 3-(4-chlorophenoxy)propyl, 1,3-

benzodioxol-5-ylmethyl, 2,3-dihydro-1*H*-inden-2-yl, 2-(morpholin-4-yl)ethyl, 3-(4-isopropylphenoxy)propyl, 3-[benzyl(butyl)amino]propyl, 3-(3,5-dipropoxyphenoxy)propyl, 2,2-diphenylethyl, 2-(1*H*-imidazol-4-yl)ethyl, 4-morpholin-4-ylbenzyl, 3-(2-methoxyethoxy)propyl, 3-morpholin-4-ylpropyl, 2-methoxyethyl, tetrahydro-2*H*-pyran-4-yl, 4-hydroxycyclohexyl, 4-methoxybenzyl, 3-(3-hydroxyphenoxy)propyl, 3-(3-acetamidophenoxy)propyl, 3-(4- *N,N*-dimethylaminocarbonylmethylphenoxy)propyl, 3-(3-carboxymethylphenoxy)propyl, 3-(3-methoxycarbonylmethylphenoxy)propyl, 3-(3-methoxycarbonylphenoxy)propyl, 3-(4-carboxymethylphenoxy)propyl, 3-(4-methoxycarbonylmethylphenoxy)propyl, 3-(3-acetylaminophenoxy)propyl, 3-(4-hydroxyphenylcarboxy)propyl, 3-(4-carboxyphenoxy)propyl, 1-(2-nitriloethyl)piperidin-4-yl, isopropyl, ethyl, 2,2-dimethylpropyl, *tert*butyl, 2-(2-methoxyethoxy)ethyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, methyl ethanoylglycinate, 2,3-dihydro-1,4-benzodioxin-6-ylmethyl, 1,3,5-trimethyl-1H-pyrazol-4-ylmethyl, 3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl, 2-(pyrrolidin-3-ylthio)ethyl, 2-[1-(*tert*butoxycarbonyl)pyrrolidin-3-yl]ethyl, 2-[1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]ethyl, 2-{[1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]thio}ethyl, 2-pyridin-2-ylethyl, 2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl, 2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl, 3-(pyridin-2-yloxy)propyl, 1-(*tert*-butoxycarbonyl)piperidin-4-yl, 1-acetylpiperidin-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-isobutyrylpiperidin-4-yl, 1-pyridin-2-ylpiperidin-4-yl, 1-(5-fluoropyridin-2-yl)piperidin-4-yl, 1-(5-chloropyridin-2-yl)piperidin-4-yl, 1-(5-methylpyridin-2-yl)piperidin-4-yl, 1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl, 1-(6-chloropyridin-3-yl)piperidin-4-yl, 1-pyridazin-3-ylpiperidin- chlorophenyl)ethyl, 3-(3-carboxyphenoxy)propyl, 3-[3-(2-methoxy-2-oxoethyl)phenoxy]propyl, 3-[4-(2-methoxy-2-oxoethyl)phenoxy]propyl, , 3-{4-[2-(dimethylamino)-2-oxoethyl]phenoxy}propyl, 3-[(4-hydroxybenzoyl)oxy]propyl, 2-{2-[(methylsulfonyl)oxy]phenoxy}ethyl, 2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl, 2-[2-(methoxycarbonyl)phenoxy]ethyl, 2-(4-chlorophenoxy)ethyl, 2-[3-(trifluoromethoxy)phenoxy]ethyl, 2-{[3-(trifluoromethoxy)phenyl]thio}ethyl, 2-(benzylamino)-2-oxoethyl or 2-{[3-(difluoromethoxy)benzyl]amino}-2-oxoethyl.4-yl, 1-(6-chloropyridazin-3-yl)piperidin-4-yl, 1-(6-methoxypyridazin-3-yl)piperidin-4-yl, 1-(4-cyanobenzyl)piperidin-4-yl, 1-[2-(trifluoromethyl)benzoyl]piperidin-4-yl, 1-[3-(methoxycarbonyl)benzyl]piperidin-4-yl, 1-benzylpiperidin-4-yl, 1-benzoylpiperidin-4-yl, 1-(phenylacetyl)piperidin-4-yl, 1-(4-cyanobenzoyl)piperidin-4-yl, 1-(3,4-difluorobenzoyl)piperidin-4-yl, 1-(2-

phenylethyl)piperidin-4-yl, 1-(2-phenylethyl)piperidin-4-yl, 1-benzylpyrrolidin-3-yl, 4-{[4-(trifluoromethyl)phenyl]thio}cyclohexyl, 1-[(5-methylisoxazol-3-yl)methyl]piperidin-4-yl, 1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl, 1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl, 2-{4-[(methylsulfonyl)oxy]phenyl}ethyl, 2-[4-(aminosulfonyl)phenyl]ethyl, 2-(4-cyanophenyl)ethyl, 2-(3-cyanophenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2-[3-(trifluoromethoxy)phenyl]ethyl, or 3-[(1-methylpiperidin-4-yl)oxy]-3-oxopropyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(3-chloro-4-methoxyphenyl)ethyl, 2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl, 2-(4-methoxyphenoxy)-2-oxoethyl, 2-[(4-methoxybenzyl)oxy]-2-oxoethyl, 2-(2-mesitylethoxy)-2-oxoethyl, 2-(2-mesityl-1-methylethoxy)-2-oxoethyl, 3-oxo-3-phenoxypropyl, 3-oxo-3-[4-(trifluoromethoxy)phenoxy]propyl, 2-{[(2,6-dimethylphenyl)acetyl]oxy}ethyl, 4-(2,6-dimethylphenoxy)-4-oxobutyl, (5-methylisoxazol-3-yl)methyl, 2-(2-aminopyridin-4-yl)ethyl, 2-pyridin-4-ylethyl, 2-pyridin-3-ylethyl, 2-(3,5-dimethylisoxazol-4-yl)ethyl or 2-(3,5-dimethyl-1*H*-pyrazol-4-yl)ethyl, or 1-pyridin-2-ylazetidin-3-yl

18. A compound selected from one or more of the following:

2-*tert*-butyl-4-({3-[3-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(2-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({3-[4-(hydroxymethyl)phenoxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N-(3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide

2-*tert*-butyl-4-{[3-(2-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-(4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)-N,N-dimethylacetamide

2-*tert*-butyl-4-{[3-(2-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

(3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-3-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

methyl (3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-4-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-cyclopentyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[3-(phenylthio)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(3-phenoxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl 3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoate

2-benzyl-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

(4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetic acid

2-*tert*-butyl-4-{[3-(3-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl (4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetate

2-*tert*-butyl-4-{[3-(4-fluorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-({1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

N-(3-{3-[(2-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}phenyl)acetamide

3-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propyl 4-hydroxybenzoate

4-(benzylamino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-[2-(3-fluorophenyl)ethyl]-5-phenyl-4-[(4-phenylbutyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

4-[(cis-4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(4-phenoxybutyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({3-[(1-oxidopyridin-3-yl)oxy]propyl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-cyclopentyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(4-methoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(4,4-difluorocyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-4-[(2-phenoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(tetrahydrofuran-2-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

4-(benzylamino)-2-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-(hexylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-5-phenyl-4-[(2-phenylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-{[4-(difluoromethoxy)benzyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(trans-4-hydroxycyclohexyl)amino]-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(3-hydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-3-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-hydroxycyclohexyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

3-{4-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}propanenitrile

2-*tert*-butyl-4-{[3-(4-chlorophenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-4-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-(2,3-dihydro-1H-inden-2-ylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(2-morpholin-4-ylethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(4-isopropylphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({3-[benzyl(butyl)amino]propyl}amino)-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3,5-dipropoxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,2-diphenylethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-ethyl-4-{[2-(1H-imidazol-4-yl)ethyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-morpholin-4-ylbenzyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-{[3-(2-methoxyethoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(3-morpholin-4-ylpropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(2-methoxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-(2-methoxyethyl)-5-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide

4-(hexylamino)-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(4-hydroxycyclohexyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(1,3-benzodioxol-5-ylmethyl)amino]-2-(2-methoxyethyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-butyl-4-[(4-methoxybenzyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

5-phenyl-4-[(4-phenylbutyl)amino]-2-(pyridin-2-ylmethyl)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3-hydroxyphenoxy)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

3-{3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propoxy}benzoic acid

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzenesulfonamide

2-*tert*-butyl-4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

tert-butyl 3-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}azetidine-1-carboxylate

2-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

4-({4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}methyl)benzonitrile

2-*tert*-butyl-4-(isopropylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

tert-butyl 3-({2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}thio)pyrrolidine-1-carboxylate

2-*tert*-butyl-5-phenyl-4-{[3-(pyridin-2-yloxy)propyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({1-[2-(trifluoromethyl)benzoyl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(5-methylpyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(6-chloropyridazin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

tert-butyl 4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidine-1-carboxylate

methyl 2-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}benzoate

methyl 3-({4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}methyl)benzoate

2-*tert*-butyl-4-{[1-(6-methoxypyridazin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({1-[(2-chloropyridin-3-yl)carbonyl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

2-*tert*-butyl-4-{[1-(6-chloropyridin-3-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(1-benzylpiperidin-4-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzenesulfonamide

4-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

2-*tert*-butyl-4-(ethylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-({1-[(5-methylisoxazol-3-yl)methyl]piperidin-4-yl}amino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N^2-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-N^1-[3-(difluoromethoxy)benzyl]glycinamide

4-[(1-benzoylpiperidin-4-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[1-(phenylacetyl)piperidin-4-yl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(1-pyridin-2-ylpiperidin-4-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(1-pyridazin-3-ylpiperidin-4-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[2-(pyridin-3-yloxy)ethyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(5-fluoropyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(2-chloro-6-methylisonicotinoyl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[1-(5-chloropyridin-2-yl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

4-({4-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]piperidin-1-yl}carbonyl)benzonitrile

2-*tert*-butyl-4-{[1-(3,4-difluorobenzoyl)piperidin-4-yl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[(1-acetylpiperidin-4-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

3-{2-[(2-isopropyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}benzonitrile

2-*tert*-butyl-5-phenyl-4-({2-[2-(trifluoromethoxy)phenyl]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}phenyl methanesulfonate

4-[(1-benzylpyrrolidin-3-yl)amino]-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-({1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]azetidin-3-yl}amino)-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

N^1-benzyl-N^2-(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinamide

2-*tert*-butyl-4-[(1-isobutyrylpiperidin-4-yl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-tert-butyl-5-phenyl-4-[(2-pyridin-2-ylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[2-(2-chlorophenyl)ethyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[1-(2-phenylethyl)piperidin-4-yl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(4-{[4-(trifluoromethyl)phenyl]thio}cyclohexyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2-{[3-(trifluoromethoxy)phenyl]thio}ethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[2-(4-chlorophenoxy)ethyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({2-[3-(trifluoromethoxy)phenoxy]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

tert-butyl 3-{2-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethoxy}azetidine-1-carboxylate

2-*tert*-butyl-4-[(2,2-dimethylpropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-(*tert*-butylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

methyl ({[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetyl}amino)acetate

2-*tert*-butyl-5-phenyl-4-(piperidin-4-ylamino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(1-methylpiperidin-4-yl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2-hydroxyethyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(biphenyl-2-ylthio)ethyl]amino}-2-*tert*-butyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[2-(pyrrolidin-3-ylthio)ethyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[(5-methyl-3-phenylisoxazol-4-yl)methyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-{[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]amino}isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-({2-[4-(trifluoromethoxy)phenyl]ethyl}amino)isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-5-phenyl-4-[(2,2,2-trifluoroethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-[(2,3-dihydroxypropyl)amino]-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

3-[(2-*tert*-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]propanenitrile

4-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(3-chloro-4-methoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{2-[(2-isobutyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl}phenyl methanesulfonate

2-isopropyl-5-phenyl-4-[(1-pyridin-2-ylpiperidin-4-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

4-(2-{[2-(4-fluorobenzyl)-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl]amino}ethyl)phenyl methanesulfonate

2-isopropyl-4-(isopropylamino)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(1-pyridin-2-ylazetidin-3-yl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-*tert*-butyl-4-{[(5-methylisoxazol-3-yl)methyl]amino}-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(4-hydroxy-3,5-dimethoxyphenyl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(2-aminopyridin-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(2-pyridin-4-ylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

2-isopropyl-5-phenyl-4-[(2-pyridin-3-ylethyl)amino]isothiazol-3(2*H*)-one 1,1-dioxide

4-{[2-(3,5-dimethylisoxazol-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide

4-[2-({2-[(5-methylisoxazol-3-yl)methyl]-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl}amino)ethyl]phenyl methanesulfonate

4-{[2-(3,5-dimethyl-1*H*-pyrazol-4-yl)ethyl]amino}-2-isopropyl-5-phenylisothiazol-3(2H)-one 1,1-dioxide

4-[2-({2-[(methylthio)methyl]-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl}amino)ethyl]phenyl methanesulfonate

2,6-Dimethylphenyl 4-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]butanoate

2-Mesitylethyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

2-[(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]ethyl (2,6-dimethylphenyl)acetate

Phenyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

4-(Trifluoromethoxy)phenyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

1-Methylpiperidin-4-yl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)-beta-alaninate

2-Mesityl-1-methylethyl [(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)amino]acetate

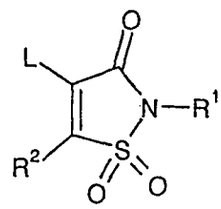
4-Methoxybenzyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

4-Methoxyphenyl N-(2-tert-butyl-1,1-dioxido-3-oxo-5-phenyl-2,3-dihydroisothiazol-4-yl)glycinate

or a pharmaceutically acceptable salt thereof.

19. A process for the preparation of a compound according to any one of claims 1-18, wherein R^1, R^2 and R^3 are as defined in claim 1, comprising the step of reacting

(a) a compound of formula (VI),



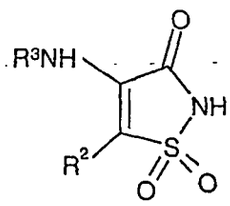
(VI)

wherein R^1 and R^2 are as defined in claim 1 and L is a leaving group such as Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, with a compound of formula (VII,

$$R^3NH_2 \text{ (VII)}$$

wherein R^3 is as defined in claim 1, optionally in the presence of an inert organic solvent such as dimethylformamide, or

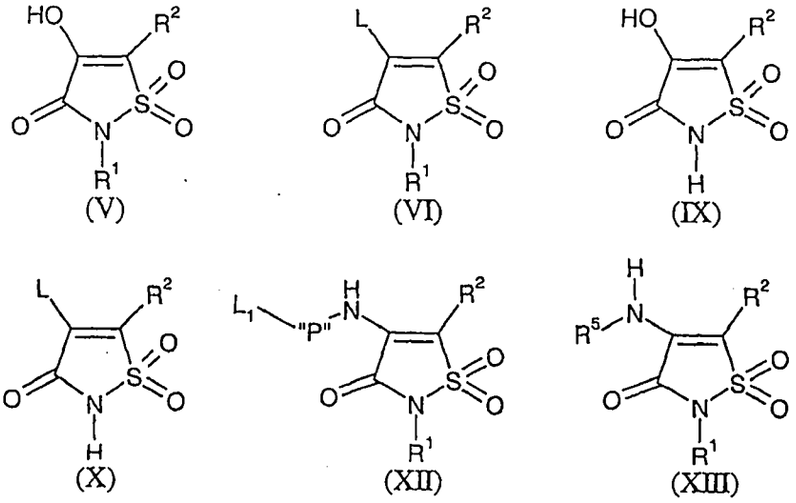
(b) a compound of formula (X),



(X)

wherein R^2 and R^3 are as defined in claim 1, either with an alkylating agent such as R^1L, wherein R^1 is defined as in claim 1 and L is a leaving group such as Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, or with R^1OH, wherein R^1 is as defined in claim 1, using Mitsunobu conditions.

20. A compound of general formula (V), (VI), (IX), (X), (XII) or (XIII)



(V) (VI) (IX)

(X) (XII) (XIII)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is defined as in claim1, R^2 is defined as in claim 1, L is a suitable leaving group such as Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, "P" is defined as for P in claim 1, L_1 is OH, NH_2, SH or a suitable leaving group such as Cl, Br, I, p-toluensulfonate, methanesulfonate or trifluoromethanesulfonate, and R^5 is Het^4 or E wherein Het^4 and E is defined as in claim 1, with the proviso that the following compounds are excluded: 4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide, 5-(4-aminophenyl)-4-hydroxy-2-methylisothiazol-3(2*H*)-one 1,1-dioxide, 4-hydroxy-2-methyl-5-(4-nitrophenyl)isothiazol-3(2*H*)-one 1,1-dioxide, 4-hydroxy-2-methyl-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide, 5-(3,4-dichlorophenyl)-4-hydroxyisothiazol-3(2*H*)-one 1,1-dioxide, 2-benzyl-4-hydroxy-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide, and 4-hydroxy-2-(4-methylphenyl)-5-phenylisothiazol-3(2*H*)-one 1,1-dioxide.

21. A pharmaceutical formulation comprising a compound according to any one of claims 1-18, or a suitable pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

22. A compound according to any one of claims 1-18, or a suitable pharmaceutically acceptable salt thereof, as a medicament in therapy.

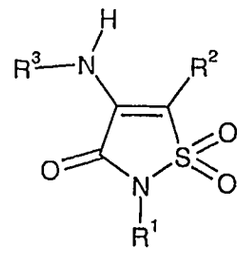
23. A compound according to any one of claims 1-18, or a suitable pharmaceutically acceptable salt thereof, for use as a medicament in treating conditions associated with a need

for modulation of nuclear hormone receptors LXR α and/or β; cardiovascular disease, atherosclerosis, hypercholesterolemia, conditions associated with a need for improving reverse cholesterol transport, conditions associated with a need for decreasing intestinal cholesterol absorption, conditions associated with a need for increasing HDL-cholesterol levels, conditions associated with a need for decreasing LDL-cholesterol levels; inflammatory conditions, Alzheimer´s disease, arteriosclerosis, type 2 diabetes, conditions associated with a need for improving HDL function, conditions associated with a need for improving HDL function; or lipid disorders (dyslipidemia) whether or not associated with insulin resistance.

24. The use of a compound according to any of claims 1-18, or a suitable pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the modulation of the nuclear hormone receptors LXR α and/or β; cardiovascular disease; atherosclerosis, hypercholesterolemia, conditions associated with a need for improving reverse cholesterol transport, conditions associated with a need for decreasing intestinal cholesterol absorption, conditions associated with a need for increasing HDL-cholesterol levels, conditions associated with a need for decreasing LDL-cholesterol levels; inflammatory conditions, Alzheimer´s disease, arteriosclerosis, type 2 diabetes, conditions associated with a need for improving HDL function, conditions associated with a need for improving HDL function; or lipid disorders (dyslipidemia) whether or not associated with insulin resistance.

25. A method of treating and/or preventing lipid disorders (dyslipidemia) whether or not associated with insulin resistance; cardiovascular disease, atherosclerosis, hypercholesterolemia, conditions associated with a need for improving reverse cholesterol transport, conditions associated with a need for decreasing intestinal cholesterol absorption, conditions associated with a need for increasing HDL-cholesterol levels, conditions associated with a need for decreasing LDL-cholesterol levels; inflammatory conditions, Alzheimer´s disease, arteriosclerosis, type 2 diabetes, or conditions associated with a need for improving HDL function comprising the administration of a thereapeutically effective amount of a compound according to any one of claims 1-18, or a suitable pharmaceutically acceptable salt thereof, to a mammal in need thereof.

The present invention relates to certain novel compounds of the formula (I)



formula (I)

to processes for preparing such compounds, to their the utility in modulation of nuclear hormone receptors Liver X Receptor (LXR) α (NR1H3) and/or β (NR1H2) and in treating and/or preventing clinical conditions including cardiovascular diseases such as atherosclerosis; inflammatory diseases, Alzheimer's disease, lipid disorders (dyslipidemias) whether or not associated with insulin resistance, type 2 diabetes and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
101613-1 WO			
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*	
PCT/SE2006/000029	9 January 2006	10 January 2005	
Applicant			
AstraZeneca AB et al			

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 6 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. ☐ 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:

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000029

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 25 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000029

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0021927 A2 (COGHLAN, M.P. ET AL), 20 April 2000 (20.04.2000) --	1-25
A	WO 0174771 A1 (SMITHKLINE BEECHAM P.L.C.), 11 October 2001 (11.10.2001) --	1-25
A	US 20030195238 A1 (A.M. GIL ET AL), 16 October 2003 (16.10.2003) --	1-25
A	WO 0103705 A1 (TULARIK INC.), 18 January 2001 (18.01.2001) --	1-25

[X] Further documents are listed in the continuation of Box C. [X] 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 2006	29-03-2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000029

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0054759 A2 (TULARIK INC.), 21 Sept 2000 (21.09.2000) --	1-25
A	WO 2004111022 A1 (GLAXO GROUP LIMITED), 23 December 2004 (23.12.2004) --	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000029

International patent classification (IPC)

C07D 275/03 (2006.01)
A61K 31/425 (2006.01)
A61K 31/427 (2006.01)
A61K 31/4427 (2006.01)
A61K 31/454 (2006.01)
A61K 31/4545 (2006.01)
A61K 31/506 (2006.01)
A61K 31/5377 (2006.01)
A61P 25/28 (2006.01)
A61P 3/06 (2006.01)
A61P 3/10 (2006.01)
A61P 9/00 (2006.01)
A61P 9/10 (2006.01)
C07D 417/12 (2006.01)

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Cited patent documents can be downloaded at www.prv.se by following the links e-tjänster/anförda dokument. Use the application number as username. The password is **ijt2qczpmm**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

31/12/2005

International application No.
PCT/SE2006/000029

WO	0021927	A2	20/04/2000	AT	284387	T	15/12/2004
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				MA	26697	A	20/12/2004
				US	6719520	B	13/04/2004
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				GB	9827521	D	00/00/0000
				GB	9827883	D	00/00/0000
				GB	9905518	D	00/00/0000
				GB	9907086	D	00/00/0000
				GB	9919362	D	00/00/0000
WO	0174771	A1	11/10/2001	AU	6215301	A	15/10/2001
				GB	0008264	D	00/00/0000
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				AU	5498101	A	20/11/2001
				BR	0110734	A	04/02/2003
				CA	2408747	A	15/11/2001
				CN	1568310	A	19/01/2005
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				EP	1286964	A	05/03/2003
				ES	2166328	A,B	01/04/2002
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				JP	2002539155	T	19/11/2002
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WO	2004111022	A1	23/12/2004	GB	0314302	D	00/00/0000

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
13 de julio de 2006 (13.07.2007)

PCT

(10) Número de Publicación Internacional
WO 2006/073366 A1

(51) Clasificación Internacional de Patentes:
C07D 275/03 (2006.01), *A61K 31/5377* (2006.01)
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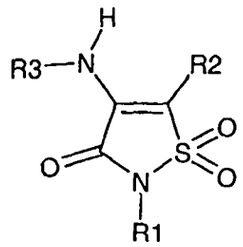
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(54) Título: DERIVADOS NO ANILÍNICOS DE 1,1-DIÓXIDOS DE ISOTIAZOL-3(2H)-ONA COMO MODULADORES DE RECEPTOR X HEPÁTICO



(I)

(57) Extracto: La presente invención se refiere a ciertos compuestos novedosos de la fórmula (I), a procesos para preparar tales compuestos, a su utilidad en la modulación de receptores hormonales nucleares Receptor X Hepático (LXR) α; (NR1H3) y/o β (NR1H2) y en tratar y/o prevenir enfermedades incluidas enfermedades cardiovasculares tales como aterosclerosis; enfermedades inflamatorias, enfermedad de Alzheimer, trastornos lipídicos (dislipidemias), asociados o no con resistencia a la insulina, diabetes tipo 2 y otras manifestaciones del síndrome metabólico, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.

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DERIVADOS NO ANILÍNICOS DE 1,1-DIÓXIDOS DE ISOTIAZOL-3(2H)-ONA COMO MODULADORES DE RECEPTOR X HEPÁTICO

Campo de la invención

La presente invención se refiere a ciertos derivados novedosos 1,1-dióxidos de 4-(amino)isotiazol-3(2H)-ona, a procesos para preparar tales compuestos, a su utilidad en la modulación de receptores hormonales nucleares: Receptor Hepático X (LXR) α (NR1H3) y/o β (NR1H2) y en tratar afecciones clínicas, incluidas enfermedades cardiovasculares, tales como arteriosclerosis; enfermedades inflamatorias, enfermedad de Alzheimer, trastornos de lípidos (dislipidemias) asociados o no con resistencia a la insulina, diabetes tipo 2; y otras manifestaciones del síndrome metabólico, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.

Antecedentes de la invención

Las anomalías de la homeostasis del colesterol y ácidos grasos, que se reflejan como diversas dislipidemias, con causa de arteriosclerosis y, por Consiguiente, enfermedad cardiovascular (CVD). Esta enfermedad es uno de los principales problemas de salud en los países industrializados y está alcanzando la misma incidencia en adultos en las naciones en desarrollo. La mayoría de los estudios muestran que las estatinas reducen el colesterol de lipoproteínas de baja densidad (LDL) en 25-30% y el riesgo relativo de episodios coronarios en aproximadamente el 30%. Aunque este efecto benéfico es significativo, efectivamente el 70% del grupo tratado permanece con un riesgo inalterado. Este hecho ha impulsado una investigación intensa con el fin de identificar otras anomalías comunes del metabolismo de lípidos que, si se trata eficientemente, podría mejorar los resultados de la actual terapia de CVD.

Los receptores hormonales nucleares LXRα y β usan oxiesteroles como ligandos naturales. Parecen actuar como sensores de colesterol con genes diana (***"target genes"***) que se requieren para la descarga de colesterol de macrófagos, como el transportador A1 de casete de unión a ATP (***"ATP binding casette transporter A1"***) (ABCA1) y apoE, al igual que productos génicos, como la proteína transferasa del éster de colesterol (CETP) y la proteína transportadora de fosfolípidos (PLTP), que se requieren para la función de lipoproteína de alta densidad (HDL) en el transporte reverso de colesterol. En el hígado, los ligandos LXR parecen estimular la secreción hepatobiliar de colesterol, una ruta controlada por el ABCG5 y ABCG8. Los mismos transportadores de colesterol parecen reducir la absorción de colesterol en enterocitos, incidiendo por lo tanto en el balance total de colesterol en el cuerpo. Estos efectos de la estimulación de LXR podrían explicar sus notables propiedades arterioscleróticas observadas en varios modelos animales.

Recientemente se ha informado que los ligandos LXR sintéticos GW3965 (Glaxo) y T-0901317 (Tularik) aumentan la tolerancia a la glucosa en ratón obeso con dieta de grasas (***"fat fed obese mouse"***), lo cual se interpretó como resultado de la gluconeogénesis hepática reducida y captación de glucosa incrementada en adipocitos. Lafitte BA *et al.*, (Proc Natl Acad Sci USA. 2003 Apr 29; 100(9):5419-24). La activación de los LXR mejora la tolerancia a la glucosa mediante la regulación coordinada del metabolismo de la glucosa en el hígado y el tejido adiposo.

JP2001163786A divulga la síntesis de ciertos 1,1-dióxidos de 2-(alquil sustituido)-4-(sustituyente)-5-(sustituyente)isotiazol-3(2*H*)-ona novedosos, en donde las posiciones 4 ó 5 se sustituyen por, verbigracia, H, alquiilo inferior o carboxilo. Se informa que estos compuestos poseen actividad inhibidora de metaloproteinasa de matriz (MMP) (especialmente actividad inhibidora de la metaloproteinasa-13 de matriz (MMP- 13)) y actividad inhibidora de agrecanasa, y son útiles en la prevención o

tratamiento de artritis (especialmente osteoartritis) y para inhibir la metástasis, infiltración o proliferación de cáncer (especialmente cáncer de mama).

EP1069110A1 divulga la síntesis de ciertos 1,1-dióxidos 2-(alquil sustituido)-4-(sustituyente)-5-(sustituyente)isotiazol-3(2H)-ona, en donde las posiciones 4 ó 5 se sustituyen por, verbigracia, H, alquilo inferior o carboxilo. Se informa que estos compuestos poseen actividad inhibidora de la metaloproteinasa-13 de matriz (MMP-13) y actividad inhibidora de aglicanasa, y son útiles para tratar trastornos artríticos tales como artritis reumatoide.

WO9708143A1 divulga la síntesis de ciertos 1,1-dióxidos de 2-(alquil sustituido)-4-(sustituyente)-5-(sustituyente)isotiazol-3(2H)-ona novedosos, en donde los sustituyentes en las posiciones 4 ó 5 se seleccionan de nitro, ciano, trifluorometilo, carbetoxi, carbometoxi, carbopropoxi, acetilo, carbamoilo, carbamoilo sustituido con un alquilo de 1 a 3 átomos de carbono, acetoxi, carboxi, hidroxi, amino, amino sustituido con un alquilo de 1 a 3 átomos de carbono, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono o halo, o las posiciones 4 y/o 5 son no sustituidas, y su uso para reducir niveles de Factor de Necrosis Tumoral (TNF) en mamíferos.

En la solicitud WO05/005417 se divulga que ciertos derivados de 1-(alquil sustituido)-3-amino-4-fenil-1*H*-pirrol-2,5-diona novedosos tienen utilidad en la modulación de receptores hormonales nucleares: Receptor Hepático X (LXR) α (NR1H3) y/o β (NR1H2) y en tratar y/o prevenir enfermedades incluidas enfermedades cardiovasculares.

En la solicitud WO05/005416 se divulga que ciertos derivados de 5-tioxo-1,5-dihidro-2H-pirrol-2-ona y 1*H*-pirrole-2,5-ditiona novedosos poseen utilidad en la modulación de receptores hormonales nucleares: Receptor

Hepático X (LXR) α (NR1H3) y/o β (NR1H2) y en tratar y/o prevenir enfermedades incluidas enfermedades cardiovasculares.

WO05/035551 divulga ciertos 1,1-dióxidos de 2-(sustituyente)-4-(sustituyente)-5-(sustituyente)isotiazol-3(2H)-ona novedosos. Se comunica que estos compuestos modulan la actividad de la proteína diana como una fosfatasa.

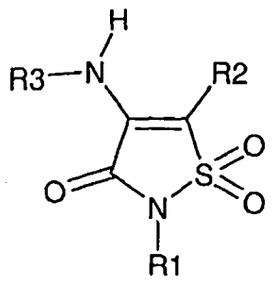
El término "modulador LXR", tal como se emplea en esta solicitud, significa más específicamente un compuesto con la capacidad de modular la actividad biológica de LXRα y/o LXRβ mediante aumento o disminución de la función y/o expresión de LXRα y/o LXRβ, donde la función LXRα y/o LXRβ puede incluir actividad reguladora de la transcripción y/o unión a proteína. La modulación puede ocurrir *in vitro* o *in vivo*. La modulación, como se describe en esta solicitud, incluye antagonismo, agonismo, antagonismo parcial y/o agonismo parcial de una función o característica asociada con LXRα y/o LXRβ, ya sea directa o indirectamente, y/o la regulación por aumento o la regulación por disminución de la expresión de LXRα y/o LXRβ, ya sea directa o indirectamente. Más específicamente, tal modulador LXR o bien potencia o bien inhibe las actividades biológicas de LXR mediante la función y/o expresión de LXR. Si tal modulador potencia parcial o completamente las actividades biológicas de LXR mediante la función y/o expresión de LXR, es un agonista LXR parcial o total, respectivamente. Es un objeto de la presente invención proveer moduladores LXR. Otro objeto de esta invención es proporcionar compuestos moduladores LXR que son agonistas LXR.

Debe observarse que para mostrar actividad en los Métodos de Prueba específicos descritos en esta solicitud, el compuesto modulador LXR tiene que unirse al dominio de unión a ligando del LXR y reclutar o bien el péptido específico derivado de la proteína co-activadora, SRC1, al complejo compuesto modulador-LXR ligado en el análisis descrito de Reclutamiento

de Co-activador, o bien uno o más de los co-factores de receptor de hormona nuclear, presentes en por ejemplo el método a base de células U2OS, descrito en esta solicitud. Los compuestos de esta invención, que forma un complejo compuesto modulador-LXR, puede reclutar por lo menos uno o más de los otros >80 co-factores diferentes conocidos de receptor de hormona nuclear en cualquier otro método a base de células, preparados y analizados de acuerdo con procedimientos conocidos. Se anticipa sin embargo que compuestos de acuerdo con fórmula (I), que no reclutan el péptido derivado de SRC1 o cualquiera de los co-factores presentes en el método a base de células descrito en esta solicitud, se unen a LXR y el complejo compuesto modulador-LXR así formado reclutará por lo menos uno o más de los demás >80 co-factores diferentes conocidos de receptor nuclear presentes en otro sistema celular. El complejo compuesto modulador-LXR puede desplazar por lo tanto co-represores, tales como NcOR, con reclutamiento simultáneo de un co-activador o puede desplazar únicamente un co-represor sin reclutamiento de co-activador, conduciendo a la activación parcial de ciertos genes regulados LXR. Péptidos reclutadores derivados de cualquiera de estos otros co-factores de receptor de hormona nuclear pueden prepararse análogamente y analizarse de acuerdo con procedimientos conocidos.

Descripción de la invención

De acuerdo con un primer aspecto de la invención se provee un compuesto de fórmula I:



Fórmula I

o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$; fenilo o heteroarilo, se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$; cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo, se sustituye cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$,

$C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

fenil Y o heteroarilY en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^2 representa

fenilo, el cual se sustituye opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o

C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3, se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$; AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$, y

E o Het^4 cada uno se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b,

$S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Las siguientes definiciones se aplicarán a todo lo largo de la especificación y las reivindicaciones anexas, a menos que específicamente se indique lo contrario:

El término "X" denota un grupo alquilo saturado o insaturado, recto o ramificado que tiene 1 a 6 átomos de carbono en donde dicho grupo alquilo puede interrumpirse opcionalmente por O, S, SiR^bR^b, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2. Se entenderá que cuando X está presente más de una vez en el mismo compuesto, entonces el valor puede ser el mismo o diferente. Ejemplos de dicho "X" incluyen, pero no se limitan a, metilo, etilo, propilo, isopropilo, butilo, *terc*-butilo, isobutilo, pentilo, hexilo, vinilo, isopropenilo, alilo, but-2-enilo, etinilo, 2-propinilo, 2-metoxietilo, 3-metilpropilo, metiltiometilo, 3-hidroxipropilo, 2-(2-metoxietoxi) etilo, 3-(2-metoxietoxi)propilo, 2,2-dimetilpropilo, 2-hidroxietilo, 2,2,2-trifluoroetilo, 2,3-dihidroxipropilo, 2-cianoetilo y metil etanoilglicinato.

El término "Y" denota un grupo alquileno, saturado o insaturado, recto o ramificado, que tiene 1 a 3 átomos de carbono en donde dicho grupo alquileno se une a nitrógeno en la posición 2 en el 1,1-dióxido de la isotiazol-3(2H)-ona y puede interrumpirse opcionalmente o terminarse por uno de los siguientes: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c y/o Y se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: OH, F, CN, NR^aR^a,

C_1-C_4alquilo, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$ o SO_2R^b. En la definición de "Y" el término "terminarse por O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c" significa que el grupo alquileno tiene como la última posición O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$ o NR^c antes de que se una adicionalmente a fenilo, heteroarilo, cicloalquilo o heterociclilo. Ejemplos de dicho "Y" incluyen, pero no se limitan a, metileno, etileno, propileno, 2-metiletileno, y 1-metiletileno.

El término "Z" denota un grupo alquileno saturado o insaturado, recto o ramificado, que tiene 1 a 6 átomos de carbono en donde dicho grupo alquileno se une a E o Het^4 y uno de los siguientes: Q, Het^1, R o Het^2, y puede interrumpirse opcionalmente o terminarse por uno de los siguientes: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $C(O)CR^a$, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, o es uno de los siguientes: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2 y/o Z se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $SiR^bR^bR^b$, $S(O)R^c$, SO_2R^c, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, OR^b. En la definición de "Z" el término "terminarse por O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2" significa que el grupo alquileno tiene como la última posición O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a o NR^aSO_2 antes de que se una adicionalmente a E, Het^4, Q, Het^1, R o Het^2. Ejemplos de dicho "Z" incluyen, pero no se limitan a, metileno, etileno, propileno, butileno, pentileno, hexileno, O, S, S(O), SO_2, C(O), OC(O), C(O)O, $C(O)CH_2$, $CH_2C(O)$, C(O)(C_1-C_4alquil), NHC(O), C(O)NH, NH, SO_2NH, $NHSO_2$, N(C_1-C_4alquil)C(O), C(O)N(C_1-C_4alquil), N(C_1-C_4alquil), $SO_2N(C_1$-C_4alquil), N(C_1-C_4alquil)SO_2, 1-metilpropileno, 2-metilpropileno y 3-metilpropileno. En la definición de Z

hay que entender que valores específicos se unen en el orden escrito, es decir, de izquierda a derecha. Por ejemplo, cuando Z es $C(O)CH_2$ entonces C(O) en dicho $C(O)CH_2$ se une a E o Het^4 y CH_2 en dicho $C(O)CH_2$ se une a Q, Het^1, R o Het^2.

El término "M" denota un anillo monocarbocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 o 8 átomos de carbono o un sistema de anillo bicíclico no aromático o parcialmente aromático, saturado o insaturado, compuesto de 8, 9 o 10 átomos de carbono. Ejemplos de dicho "M" incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctanilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclopentadienilo, ciclohexadienilo, ciclooctadienilo, decalina, hidrindano, indano, indeno, y biciclo[4.2.0]octa-1,3,5-trieno.

El término "E" denota un anillo monocarbocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 o 8 átomos de carbono o un sistema de anillo bicíclico no aromático o parcialmente aromático, saturado o insaturado, compuesto de 8, 9 o 10 átomos de carbono. El anillo se une, a menos que se indique lo contrario, a través de su parte no aromática a nitrógeno en la posición 4 en el 1,1-dióxido de la isotiazol-3(2*H*)-ona. Ejemplos de dicho "E" incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctanilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclopentadienilo, ciclohexadienilo, ciclooctadienilo, decalina, hidrindano, indano, indeno y biciclo[4.2.0]octa-1,3,5-trieno.

El término "A" denota un anillo monocíclico aromático, compuesto de 6 átomos de carbono o un sistema de anillo bicíclico aromático, compuesto de 10 átomos de carbono. Ejemplos de dicho "A" incluyen, pero no se limitan a, fenilo, naftaleno y azuleno.

El término "P" denota un grupo alquileno saturado o insaturado, recto o ramificado, que tiene 1 a 6 átomos de carbono en donde el grupo alquileno se une a nitrógeno en la posición 4 en el 1,1-dióxido de la isotiazol-3(2*H*)-ona y se interrumpe o termina opcionalmente por uno de los siguientes: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 y/o P se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o OR^b. En la definición de "P" el término "se termina por O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2" significa que el grupo alquileno tiene como la última posición O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2" antes de que se una adicionalmente a M, Het^3, A o Het^5. Ejemplos de dicho "P" incluyen, pero no se limitan a, metileno, etileno, propileno, butileno, etilenoxi, propilenoxi, butilenoxi, etilenamino, etilentio, propilentio, $CH_2C(O)NHCH_2$, $CH_2C(O)O$, $CH_2CH_2C(O)O$-$CH_2CH_2CH_2C(O)O$, $CH_2C(O)OCH_2$, $CH_2C(O)OCH_2CH_2$, $CH_2CH_2OCOCH_2$, $CH_2C(O)OCH(CH_3)CH_2$, 1-metilpropileno, 2-metilpropileno y 3- metilpropileno. En la definición de P hay que entender que valores específicos se unen en el orden escrito, es decir, de izquierda a derecha. Por ejemplo, cuando P es etilenoxi entonces es el oxígeno el que se une a M, Het^3, A o Het^5.

El término "Q" denota un anillo monocíclico no aromático, saturado o insaturado compuesto de 3, 4, 5, 6, 7 o 8 átomos de carbono, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye

opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$. Ejemplos de dicho "Q" incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctanilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclopentadienilo, ciclohexadienilo y ciclooctadienilo.

El término "R" denota un grupo fenilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a- OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

El término "T" denota metileno o es uno de los siguientes: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2. T se une a M, Het^3, A o Het^5 y uno de los siguientes: Q, Het^1, R o Het^2. Ejemplos de dicho "T" incluyen, pero no se limitan a, metileno, O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a y NR^aSO_2.

El término "C_1alquilo" denota un grupo alquilo que tiene 1 átomo de carbono. Un ejemplo de dicho alquilo incluye, pero no se limita a, metilo.

El término "C_1-C_3alquilo" denota un grupo alquilo, saturado o insaturado, recto o ramificado, que tiene 1 a 3 átomos de carbono. Ejemplos de dicho

alquilo incluyen, pero no se limitan a, metilo, etilo, propilo, isopropilo, vinilo, isopropenilo, alilo, etinilo, y 2-propinilo.

El término "C_1-C_3alquilo" denota es un grupo alquilo saturado o insaturado, recto o ramificado, que tiene 1 a 4 átomos de carbono. Ejemplos de dicho alquilo incluyen, pero no se limitan a, metilo, etilo, propilo, isopropilo, *terc*-butilo, vinilo, isopropenilo, alilo, but-2-enilo, etinilo, 2-propinilo, y but-2-inilo.

El término "halógeno" denota grupos fluoro, cloro, bromo y yodo.

El término "cicloalquilo" denota un anillo monocíclico no aromático, saturado o insaturado compuesto de 3, 4, 5, 6, 7 o 8 átomos de carbono. Por ejemplo, C_3-C_6cicloalquilo denota un anillo monocíclico no aromático, saturado o insaturado compuesto de 3, 4, 5 o 6 átomos de carbono, por ejemplo ciclopropilo, ciclobutilo, ciclopentilo o ciclohexil. Otros ejemplos de dicho "cicloalquilo" incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctanilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclopentadienilo, ciclohexadienilo y ciclooctadienilo.

El término "heterociclilo" denota un anillo monocíclico de 3, 4, 5, 6, 7 u 8 miembros, no aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono independientemente seleccionado de uno o más de, por ejemplo, nitrógeno, oxígeno o azufre. El término "azufre" se entenderá que incluye sulfóxido (S(O)) y sulfona (SO_2). El término "nitrógeno" se entenderá que incluye óxido de nitrógeno (NO). Ejemplos de dicho "heterociclilo" incluyen, pero no se limitan a, aziridina, azetidina, 2-pirrolina, 3-pirrolina, pirrolidina, imidazolina, piperidina, piperazina, 2-pirazolina, oxirano, oxetano, tetrahidrofurano, tetrahidropirano, 1,4-dioxano, 1,3-dioxolano, 1,2-oxatiolano, morfolina, 3-

pirazolina, pirazolidina, 2H-pirano, 4H-pirano, 1,4-ditiano, 1,4-oxatiano y tiomorfolina.

El término "heteroarilo" denota un anillo monocíclico de 5 ó 6 miembros, aromático, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono independientemente seleccionado de uno o más de, por ejemplo, nitrógeno, oxígeno y azufre. El término "azufre" se entenderá que incluye sulfóxido (S(O)) y sulfona (SO_2). El término "nitrógeno" se entenderá que incluye óxido de nitrógeno (NO). Ejemplos de dicho "heteroarilo" incluyen, pero no se limitan a, furano, pirrol, pirazina, pirazol, imidazol, triazol, pirimidina, piridazina, piridina, piridin-1-óxido, isoxazol, oxazol, isotiazol, tiazol, tiofeno, 1,2,4-triazol, furazano, 1,2,3-oxadiazol, 1,2,4-oxadiazol, 1,2,5-oxadiazol, 1,3,4-oxadiazol, 1,2,5-tiadiazol, 1,2,4-tiadiazol y 1,2,3-tiadiazol.

El término "Het^1" denota un anillo monocíclico de 3, 4, 5, 6, 7, 8, 9, o 10 miembros, no aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono independientemente seleccionado de uno o más de por ejemplo nitrógeno, oxígeno o azufre, y en donde el anillo se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$. El término "azufre" se entenderá que incluye sulfóxido (S(O)) y sulfona (SO_2). El término "nitrógeno" se entenderá que incluye óxido de nitrógeno (NO). Ejemplos de dicho "Het^1" incluyen, pero no se limitan a, aziridina, azetidina, 2-pirrolina, 3-pirrolina, pirrolidina, imidazolina, piperidina,

piperazina, 2-pirazolina, oxirano, oxetano, tetrahidrofurano, tetrahidropirano, 1,4-dioxano, 1,3-dioxolano, 1,2-oxatiolano, morfolina, 3-pirazolina, pirazolidina, 2H-pirano, 4H-pirano, 1,4-ditiano, 1,4-oxatiano y tiomorfolina.

El término "Het^2" denota un anillo monocíclico de 5 ó 6 miembros, aromático, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono independientemente seleccionado de uno o más de por ejemplo nitrógeno, oxígeno y azufre, y el cual se sustituye por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$. El término "azufre" se entenderá que incluye sulfóxido (S(O)) y sulfona (SO_2). El término "nitrógeno" se entenderá que incluye óxido de nitrógeno (NO). Ejemplos de dicho "Het^2" incluyen, pero no se limitan a, furano, pirrol, pirazina, pirazol, imidazol, triazol, pirimidina, piridazina, piridina, piridin-1-óxido, isoxazol, oxazol, isotiazol, tiazol, tiofeno, 1,2,4-triazol, furazano, 1,2,3-oxadiazol, 1,2,4-oxadiazol, 1,2,5-oxadiazol, 1,3,4-oxadiazol, 1,2,5-tiadiazol, 1,2,4-tiadiazol y 1,2,3- tiadiazol.

El término "Het^3" denota un anillo monocíclico de 3, 4, 5, 6, 7, 8, 9 ó 10 miembros, no aromático, saturado o insaturado o un sistema de anillo bicíclico de 9 ó 10 miembros, no aromático o parcialmente aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo monocíclico o sistema de anillo bicíclico es un elemento distinto de carbono seleccionado independientemente de uno o más de por ejemplo nitrógeno, oxígeno o azufre. El término "azufre" se entenderá que incluye sulfóxido

(S(O)) y sulfona (SO_2). El término "nitrógeno" se entenderá que incluye óxido de nitrógeno (NO). Ejemplos de dicho "Het^3" incluyen, pero no se limitan a aziridina, azetidina, 2-pirrolina, 3-pirrolina, pirrolidina, imidazolina, piperidina, piperazina, 2-pirazolina, oxirano, oxetano, tetrahidrofurano, tetrahidropirano, 1,4-dioxano, 1,3-dioxolano, 1,2-oxatiolano, morfolina, 3-pirazolina, pirazolidina, 2H-pirano, 4H-pirano, 1,4-ditiano, 1,4-oxatiano, tiomorfolina, indolina, 1,3-dihidro-2-benzofurano, 2,3-dihidro-1-benzofurano, 1,3-benzodioxol, 2,3-dihidro-1,4-benzodioxina, cromano e isocromano.

El término "Het^4" denota un anillo monocíclico de 3, 4, 5, 6, 7, 8, 9 ó 10 miembros, no aromático, saturado o insaturado o un sistema de anillo bicíclico de 9 ó 10 miembros, no aromático o parcialmente aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo monocíclico o sistema de anillo bicíclico es un elemento distinto de carbono seleccionado independientemente de uno o más de, por ejemplo, nitrógeno, oxígeno o azufre. El término "azufre" se entenderá que incluye sulfóxido (S(O)) y sulfona (SO_2). El término "nitrógeno" se entenderá que incluye óxido de nitrógeno (NO). El anillo se une, a menos que se especifique lo contrario, a través de su parte no aromática, a nitrógeno en la posición 4 en el 1,1-dióxido de la isotiazol-3(2*H*)-ona. Ejemplos de dicho "Het^4" incluyen, pero no se limitan a, aziridina, azetidina, 2-pirrolina, 3-pirrolina, pirrolidina, imidazolina, piperidina, piperazina, 2-pirazolina, oxirano, oxetano, tetrahidrofurano, furano, tetrahidropirano, 1,4-dioxano, 1,3-dioxolano, 1,2-oxatiolano, morfolina, 3-pirazolina, pirazolidina, isoxazol, 2H-pirano, 4H-pirano, 1,4-ditiano, 1,4-oxatiano, tiomorfolina, indolina, 1,3-dihidro-2-benzofurano, 2,3-dihidro-1-benzofurano, 1,3-benzodioxol, 2,3-dihidro-1,4-benzodioxina, cromano e isocromano.

El término "Het^5" denota un anillo monocíclico de 5 ó 6 miembros, aromático, o un anillo bicíclico de 9 ó 19 miembros, aromático, en el cual uno o más de los átomos en el anillo monocíclico o sistema de anillo

bicíclico es un elemento distinto de carbono seleccionado independientemente de uno o más de por ejemplo nitrógeno, oxígeno o azufre. El término "azufre" se entenderá que incluye sulfóxido (S(O)) y sulfona (SO_2). El término "nitrógeno" se entenderá que incluye óxido de nitrógeno (NO). Ejemplos de dicho "Het^5" incluyen, pero no se limitan a, furano, pirrol, pirazina, pirazol, imidazol, triazol, pirimidina, piridazina, piridina, piridin-1-óxido, isoxazol, oxazol, isotiazol, tiazol, tiofeno, 1,2,4-triazol, furazano, 1,2,3-oxadiazol, 1,2,4-oxadiazol, 1,2,5-oxadiazol, 1,3,4-oxadiazol, 1,2,5-tiadiazol, 1,2,4-tiadiazol, 1,2,3-tiadiazol, benzofurano, isobenzofurano, indol, isoindol, benzotiofeno, benzo[c]tiofeno, benzimidazol, purina, indazol, benzoxazol, benzisoxazol, benztiazol, quinolina, quinoxalina, quinazolina, cinnolina e isoquionolina.

R^a representa independientemente H o una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.
R^b representa independientemente una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.
R^c representa independientemente H o una cadena C_1-C_3alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.

Se entenderá que cuando un sustituyente lleva más de uno de R^a, R^b o R^c, entonces cada uno de estos puede ser el mismo o diferente. Por ejemplo, NR^aR^a incluye amino, alquilamino y dialquilamino. Más aún, se entenderá que cuando diferentes sustituyentes en el mismo compuesto llevan más de uno de R^a, R^b o R^c, entonces cada uno de estos puede ser el mismo o diferente.

Seguirán ahora otros valores de R^a, R^b y R^c en compuestos de fórmula I. Se entenderá que tales valores pueden usarse, donde se considere apropiado, con cualquiera de las definiciones, reivindicaciones o incorporaciones ya definidas o definidas más adelante.

En un primer grupo de compuestos de fórmula I

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$; cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

fenilo o heteroarilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^2 representa

Fenilo, el cual se sustituye opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^3R^3$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^bC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 cada uno se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$,

$NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En un segundo grupo de compuestos de fórmula I

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b o $C(O)R^b$;

cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b o $C(O)R^b$;

fenilo o heteroarilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 representa

fenilo, que se sustituye opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

R^3 es el mismo como en el primer grupo de compuestos de fórmula I.

En un tercer grupo de compuestos de fórmula I

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$,

R^2 es el mismo que en el segundo grupo de compuestos de fórmula I,

R^3 es el mismo que en el primer grupo de compuestos de fórmula I.

En un cuarto grupo de compuestos de fórmula I

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b o $C(O)R^b$,

R^2 es el mismo que en el segundo grupo de compuestos de fórmula I,

R^3 es el mismo que en el primer grupo de compuestos de fórmula I.

En un quinto grupo de compuestos de fórmula I

R^1 es el mismo que en el primer grupo de compuestos de fórmula I,

R^2 es el mismo que en el primer grupo de compuestos de fórmula I, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$,

$OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En un sexto grupo de compuestos de fórmula I

R^1 es el mismo que en el primer grupo de compuestos de fórmula I,

R^2 es el mismo que en el primer grupo de compuestos de fórmula I, y

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o

C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En un séptimo grupo de compuestos de fórmula I

R^1 es el mismo que en el primer grupo de compuestos de fórmula I,

R^2 es el mismo que en el primer grupo de compuestos de fórmula I, y

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En un octavo grupo de compuestos de fórmula I

R^1 es el mismo que en el segundo grupo de compuestos de fórmula I,

R^2 es el mismo que en el segundo grupo de compuestos de fórmula I, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En un noveno grupo de compuestos de fórmula I

R^1 es el mismo que en el segundo grupo de compuestos de fórmula I,

R^2 es el mismo que en el segundo grupo de compuestos de fórmula I, y

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_2alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$,

$C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En un décimo grupo de compuestos de fórmula I

R^1 es el mismo que en el segundo grupo de compuestos de fórmula I, R^2 es el mismo que en el segundo grupo de compuestos de fórmula I, y R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

En un undécimo grupo de compuestos de fórmula I

R^1 es el mismo que en el tercer grupo de compuestos de fórmula I,

R^2 es el mismo que en el tercer grupo de compuestos de fórmula I, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En un duodécimo grupo de compuestos de fórmula I

R^1 es el mismo que en el tercer grupo de compuestos de fórmula I,

R^2 es el mismo que en el tercer grupo de compuestos de fórmula I, y

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b,

SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En un décimo tercer grupo de compuestos de fórmula I

R^1 es el mismo que en el tercer grupo de compuestos de fórmula I,

R^2 es el mismo que en el tercer grupo de compuestos de fórmula I, y

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

En un décimo cuarto grupo de compuestos de fórmula I

R^1 es el mismo que en el cuarto grupo de compuestos de fórmula I,

R^2 es el mismo que en el cuarto grupo de compuestos de fórmula I, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En un décimo quinto grupo de compuestos de fórmula I

R^1 es el mismo que en el cuarto grupo de compuestos de fórmula I,

R^2 es el mismo que en el cuarto grupo de compuestos de fórmula I, y

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En un décimo sexto grupo de compuestos de fórmula I

R^1 es el mismo que en el cuarto grupo de compuestos de fórmula I,

R^2 es el mismo que en el cuarto grupo de compuestos de fórmula I, y

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Los compuestos de fórmula I tienen actividad como medicamentos. En particular, los compuestos de fórmula (I) son agonistas LXR.

En otro aspecto de la invención, se provee un compuesto de acuerdo con la fórmula (V) en la cual R^1 se selecciona de etilo, isopropilo, n-butilo, *terc*-butilo, ciclopentilo, hexilo, bencilo, 2-metoxietilo, piridin-2-ilmetilo, piridin-3-ilmetilo, piridin-4-ilmetilo, tetrahidrofuran-2-ilmetilo o 2-(3-fluorofenil)etilo; y R^2 es fenilo.

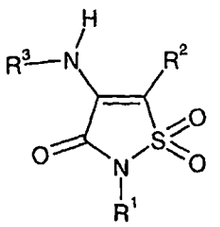
En otro aspecto de la invención, se provee un compuesto de acuerdo con la fórmula (VI) en la cual R^1 se selecciona de etilo, isopropilo, n-butilo, *terc*-butilo, ciclopentilo, hexilo, bencilo, 2-metoxietilo, piridin-2-ilmetilo, piridin-3-ilmetilo, piridin-4-ilmetilo, tetrahidrofuran-2-ilmetilo o 2-(3-fluorofenil)etilo,
R^2 es fenilo y L es un grupo saliente como por ejemplo Cl, Br, I, metanosulfonato (MsO) o trifluorometanosulfonato (OTf).

En un aspecto de la invención se provee un compuesto de fórmula (I) en la cual R^1 se selecciona de etilo, isopropilo, n-butilo, *terc*-butilo, ciclopentilo, hexilo, bencilo, 2-metoxietilo, piridin-2-ilmetilo, piridin-3-ilmetilo, piridin-4-ilmetilo, tetrahidrofuran-2-ilmetil o 2-(3-fluorofenil)etilo;
R^2 es fenilo; y
R^3 se selecciona de butilo, hexilo, bencilo, 3-[3-(hidroximetil)fenoxi] propilo, 4-fenilbutilo, 3-(2-metoxifenoxi)propilo, 3-[4-(hidroximetil)fenoxi] propilo, 3-(2-fluorofenoxi)propilo, 3-(2-clorofenoxi) propilo, 3-(3-metoxifenoxi)propilo, 3-(piridin-3-iloxi)propilo, 3-(piridin-4-iloxi)propilo, 1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 3-(feniltio)propilo, 3-fenoxipropilo, 3-(3-clorofenoxi)propilo, 3-(3- fluorofenoxi)propilo, 3-(4-fluorofenoxi)propilo, 1-[4-(trifluorometil)pirimidin-2-il]piperidin-4-ilo, *cis*-4-hidroxiciclohexilo, 4-fenoxibutilo, 3-[(1-oxidopiridin-3-il)oxi]propilo, 3-(4-metoxifenoxi)propilo, 4,4-difluorociclohexilo, 2-fenoxietilo, 2-feniletilo, 4-(difluorometoxi)bencilo, *trans*-4-hidroxiciclohexilo, 3-hidroxipropilo,

2,3-dihidro-1,4-benzodioxin-2-ilmetilo, 4-hidroxiciclohexilo, 3-(4-clorofenoxi)propilo, 1,3-benzodioxol-5-ilmetilo, 2,3-dihidro-1H-inden-2-ilo, 2-(morfolin-4-il)etilo, 3-(4-isopropilfenoxi)propilo, 3-[bencil(butil) amino]propilo, 3-(3,5-dipropoxifenoxi)propilo, 2,2-difeniletilo, 2-(1*H*-imidazol-4-il) etil 4-morfolin-4-ilbencilo, 3-(2-metoxietoxi)propilo, 3-morfolin-4-ilpropilo, 2-metoxietilo, tetrahidro-2*H*-piran-4-ilo, 4-hidroxiciclohexilo, 4-metoxibencilo, 3-(3-hidroxifenoxi)propilo, 3-(3-acetamidofenoxi)propilo, 3-(4-*N*,*N*-dimetilaminocarbonilmetilfenoxi) propilo, 3-(3-carboximetilfenoxi)propilo, 3-(3-metoxicarbonilmetilfenoxi) propilo, 3-(3-metoxicarbonilfenoxi)propilo, 3-(4-carboximetilfenoxi) propilo, 3-(4-metoxicarbonilmetilfenoxi)propilo, 3-(3-acetilaminofenoxi) propilo, 3-(4-hidroxifenilcarboxi)propilo, 3-(4-carboxifenoxi)propilo o 1-(2-nitriloetil)piperidin-4-ilo.

Otras incorporaciones de la invención

De acuerdo con otra incorporación de la invención se provee un compuesto de la fórmula general (I)



fórmula (I)

o su sal farmacéuticamente aceptable,

en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F,

OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

o R^1 es cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es fenilo o heteroarilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes independientemente seleccionados de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye

opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^2 representa

fenilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

o R^3 es MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$ $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$,

$NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Seguirán ahora otros valores de R^1, R^2 y R^3. Se entenderá que tales valores pueden utilizarse donde se considere apropiado con cualquiera de las definiciones, reivindicaciones o incorporaciones ya definidas o definidas más adelante.

En una primera incorporación de la invención se provee una clase de compuestos de fórmula I en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

o R^1 es cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-

C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es fenilo o heteroarilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno

(Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^2 representa

fenilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F,

OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

o R^3 es MP o Het^3P en donde M y Het^3 se sustituye cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$ $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$,

$C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una segunda incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o $C(O)R^b$;

o R^1 es cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o $C(O)R^b$;

o R^1 es fenilo o heteroarilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

o R^1 es cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b,

$C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

o R^1 es fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 representa

fenilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

R^3 es el mismo que para la primera incorporación.

En una tercera incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F,

OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$,

R^2 es el mismo que para la segunda incorporación, y

R^3 es el mismo que para la primera incorporación.

En una cuarta incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o $C(O)R^b$,

R^2 es el mismo que para la segunda incorporación, y

R^3 es el mismo que para la primera incorporación.

En una quinta incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la primera incorporación,

R^2 es el mismo que para la primera incorporación, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En una sexta incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la primera incorporación,

R^2 es el mismo que para la primera incorporación, y

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una séptima incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la primera incorporación,

R^2 es el mismo que para la primera incorporación, y

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 cada uno se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una octava incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la segunda incorporación,

R^2 es el mismo que para la segunda incorporación, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En una novena incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la segunda incorporación,

R^2 es el mismo que para la segunda incorporación, y

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituye cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$,

$C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una décima incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la segunda incorporación,

R^2 es el mismo que para la segunda incorporación, y

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$,

OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una undécima incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la tercera incorporación,

R^2 es el mismo que para la tercera incorporación, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En una duodécima incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la tercera incorporación,

R^2 es el mismo que para la tercera incorporación, y

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una décima tercera incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la tercera incorporación,

R^2 es el mismo que para la tercera incorporación, y

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una décimocuarta incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la cuarta incorporación,

R^2 es el mismo que para la cuarta incorporación, y

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

En una décimoquinta incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la cuarta incorporación,

R^2 es el mismo que para la cuarta incorporación, y

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a,

OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una décimosexta incorporación de la invención se provee una clase de compuestos de fórmula (I) en donde

R^1 es el mismo que para la cuarta incorporación,

R^2 es el mismo que para la cuarta incorporación, y

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1 , Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Los compuestos de fórmula (I) poseen actividad como medicamentos. En particular, los compuestos de fórmula (I) son agonistas LXR.

Compuestos específicos de la invención son uno o más de los siguientes:

1,1-dióxido de 2-*terc*-butil-4-({3-[3-(hidroximetil)fenoxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({3-[4-(hidroximetil)fenoxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

N-(3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetamida

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

2-(4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)-N,N-dimetilacetamida

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4- {[3-(3-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

ácido (3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acético

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-3-iloxi)propil]amino}isotiazol-3(2*H*)-ona

metil (3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

1,1-dióxido de 2-*terc*-butil-5 -fenil-4-{[3-(piridin-4-iloxi)propil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-*terc*-butil-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il}amino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-ciclopentil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(feniltio)propil]amino}isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(3-fenoxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

metil 3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}benzoato

1,1-dióxido de 2-bencil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

ácido (4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acético

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

metil (4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-({1-[4-(trifluorometil)pirimidin-2-il] piperidin-4-il}amino)isotiazol-3(2*H*)-ona

N-(3-{3-[(2-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] propoxi}fenil)acetamida

3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] propil 4-hidroxibenzoato

1,1-dióxido de 4-(bencilamino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-[2-(3-fluorofenil)etil]-5-fenil-4-[(4-fenilbutil)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(*cis*-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(4-fenoxibutil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({3-[(1-oxidopiridin-3-il)oxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-ciclopentil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(4,4-difluorociclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(tetrahidrofuran-2-ilmetil) isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-(hexilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-{[4-(difluorometoxi)bencil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(trans-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(3-hidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-3-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,3-dihidro-1,4-benzodioxin-2-ilmetil) amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-hidroxiciclohexil)amino]-5-fenilisotiazol-3(2*H*)-ona

ácido 4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoico

3-{4-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}propanonitrilo

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-4-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-(2,3-dihidro-1H-inden-2-ilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(2-morfolin-4-iletil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-isopropilfenoxi)propil]amino}-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 4-({3-[bencil(butil)amino]propil}amino)-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3,5-dipropoxifenoxi)propil]amino}-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,2-difeniletil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-etil-4-{[2-(1H-imidazol-4-il)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-morfolin-4-ilbencil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-{[3-(2-metoxietoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(3-morfolin-4-ilpropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(2-metoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-(2-metoxietil)-5-fenil-4-(tetrahidro-2H-piran-4-ilamino)isotiazol-3 (2*H*)-ona

1,1-dióxido de 4-(hexilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(4-hidroxiciclohexil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-metoxibencil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-2-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-hidroxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

ácido 3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}benzoico

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenilmetanosulfonato

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}bencenosulfonamida

1,1-dióxido de 2-*terc*-butil-4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il}amino)-5-fenilisotiazol-3(2*H*)-ona

terc-butil 3-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}azetidin-1-carboxilato

2-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenilmetanosulfonato

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

4-({4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}metil)benzonitrilo

1,1-dióxido de 2-*terc*-butil-4-(isopropilamino)-5-fenilisotiazol-3(2*H*)-ona

4-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenil metanosulfonato

terc-butil 3-({2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}tio)pirrolidin-1-carboxilato

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-2-iloxi)propil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2-{[3-cloro-5-(trifluorometil)piridin-2-il] amino}etil) amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({1-[2-(trifluorometil)benzoil] piperidin-4-il}amino)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(5-metilpiridin-2-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(6-cloropiridazin-3-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

terc-butil 4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-carboxilato

metil 2-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}benzoato

metil 3-({4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-il}metil)benzoato

1,1-dióxido de 2-*terc*-butil-4-{[1-(6-metoxipiridazin-3-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({1-[(2-cloropiridin-3-il)carbonil]piperidin-4-il}amino)-5-fenilisotiazol-3(2*H*)-ona

2-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenilmetanosulfonato

1,1-dióxido de 2-*terc*-butil-4-{[1-(6-cloropiridin-3-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1-bencilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

4-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}bencenosulfonamida

4-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

1,1-dióxido de 2-*terc*-butil-4-(etilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil]-4-({1-[(5-metilisoxazol-3-il)metil]piperidin-4-il}amino)-5-fenilisotiazol-3(2*H*)-ona

N^2-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-N^1-[3-(difluorometoxi)bencil]glicinamida

1,1-dióxido de 4-[(1-benzoilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[1-(fenilacetil)piperidin-4-il]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(1-piridin-2-ilpiperidin-4-il)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(1-piridazin-3-ilpiperidin-4-il)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[2-(piridin-3-iloxi)etil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(5-fluoropiridin-2-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3,5-dimetil-1H-pirazol-1-il)propil] amino}-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(2-cloro-6-metilisonicotinoil)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(5-cloropiridin-2-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({1-[4-(trifluorometil)piridin-2-il]piperidin-4-il}amino)isotiazol-3(2*H*)-ona

4-({4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}carbonil)benzonitrilo

1,1-dióxido de 2-*terc*-butil-4-{[1-(3,4-difluorobenzoil)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1-acetilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

3-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[2-(trifluorometoxi)fenil]etil} amino)isotiazol-3 (2*H*)-ona

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenilmetanosulfonato

1,1-dióxido de 4-[(1-bencilpirrolidin-3-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-il} amino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

N^1-bencil-N^2-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinamida

1,1-dióxido de 2-*terc*-butil-4-[(1-isobutirilpiperidin-4-il)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-piridin-2-iletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[2-(2-clorofenil)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[1-(2-feniletil)piperidin-4-il]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[3-(trifluorometil)fenil]etil}amino) isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(4-{[4-(trifluorometil)fenil]tio} ciclohexil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-{[3-(trifluorometoxi)fenil]tio}etil) amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[2-(4-clorofenoxi)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({1-[5-(trifluorometil)piridin-2-il]piperidin-4-il} amino)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[3-(trifluorometoxi)fenoxi]etil} amino)isotiazol-3(2*H*)-ona

terc-butil 3-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etoxi}azetidin-1-carboxilato

1,1-dióxido de 2-*terc*-butil-4-[(2,2-dimetilpropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-(*terc*-butilamino)-5-fenilisotiazol-3(2*H*)-ona

metil ({[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]acetil}amino)acetato

1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(1-metilpiperidin-4-il)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2-hidroxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(bifenil-2-iltio)etil]amino}-2-*terc*-butil-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[2-(pirrolidin-3-iltio)etil]amino} isotiazol-3 (2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[(5-metil-3-fenilisoxazol-4-il)metil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[(1,3,5-trimetil-1H-pirazol-4-il)metil] amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-{[5-(trifluorometil)piridin-2-il]oxi} etil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[4-(trifluorometoxi)fenil]etil} amino) isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2,2,2-trifluoroetil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,3-dihidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] propanenitrilo

1,1-dióxido de 4-{[2-(3,4-dimetoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 4-{[2-(3-cloro-4-metoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

4-{2-[(2-isobutil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenilmetanosulfonato

1,1-dióxido de 2-isopropil-5-fenil-4-[(1-piridin-2-ilpiperidin-4-il)amino] isotiazol-3(2*H*)-ona

4-(2-{[2-(4-fluorobencil)-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il]amino}etil)fenilmetanosulfonato

1,1-dióxido de 2-isopropil-4-(isopropilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(1-piridin-2-ilazetidin-3-il)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[(5-metilisoxazol-3-il)metil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(4-hidroxi-3,5-dimetoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(2-aminopiridin-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(2-piridin-4-iletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(2-piridin-3-iletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(3,5-dimetilisoxazol-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

4-[2-({2-[(5-metilisoxazol-3-il)metil]-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il}amino)etil]fenilmetanosulfonato

1,1-dióxido de 4-{[2-(3,5-dimetil-1*H*-pirazol-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2H)-ona

4-[2-({2-[(metiltio)metil]-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il}amino)etil]fenilmetanosulfonato

2,6-dimetilfenil 4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]butanoato

2-mesitiletil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato

2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] etil (2,6-dimetilfenil)acetato
fenil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato
4-(trifluorometoxi)fenil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato
1-metilpiperidin-4-il N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato
2-mesitil-1-metiletil [(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]acetato
4-metoxibencil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato
4-metoxifenil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato
o su sal farmacéuticamente aceptable.

En un aspecto de la invención, se provee un compuesto de fórmula (I) en la cual R^1 se selecciona de etilo, isopropilo, n-butilo, *terc*-butilo, ciclopentilo, hexilo, bencilo, 2-metoxietilo, piridin-2ilmetilo, piridin-3-ilmetilo, piridin-4-ilmetilo, tetrahidrofuran-2-ilmetilo o 2-(3-fluorofenil)etilo;
R^2 es fenilo; y
R^3 se selecciona de n-butilo, n-hexilo, bencilo, 3-[3-(hidroximetil)fenoxi] propilo, 4-fenilbutilo, 3-(2-metoxifenoxi)propilo, 3-[4-(hidroximetil) fenoxi]propilo, 3-(2-fluorofenoxi)propilo, 3-(2-clorofenoxi)propilo, 3-(3-metoxifenoxi)propilo, 3-(piridin-3-iloxi)propilo, 3-(piridin-4-iloxi)propilo, 1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 3-(feniltio)propilo, 3-fenoxipropilo, 3-(3-clorofenoxi)propilo, 3-(3- fluorofenoxi)propilo, 3-(4-fluorofenoxi)propilo, 1-[4-(trifluorometil)pirimidin-2-il]piperidin-4-ilo, *cis*-4-hidroxiciclohexilo, 4-fenoxibutilo, 3-[(1-oxidopiridin-3-il)oxi]propilo, 3-(4-metoxifenoxi)propilo, 4,4-difluorociclohexilo, 2-fenoxietilo, 2-feniletilo, 4-(difluorometoxi)bencilo, *trans*-4-hidroxiciclohexilo, 3-hidroxipropilo, 2,3-dihidro-1,4-benzodioxin-2-ilmetilo, 4-hidroxiciclohexilo, 3-(4-

clorofenoxi)propilo, 1,3-benzodioxol-5-ilmetilo, 2,3-dihidro-1*H*-inden-2-ilo, 2-(morfolin-4-il)etilo, 3-(4-isopropilfenoxi)propilo, 3-[bencil(butil) amino]propilo, 3-(3,5-dipropoxifenoxi)propilo, 2,2-difeniletilo, 2-(1*H*-imidazol-4-il)etilo, 4-morfolin-4-ilbencilo, 3-(2-metoxietoxi)propilo, 3-morfolin-4-ilpropilo, 2-metoxietilo, tetrahidro-2*H*-piran-4-ilo, 4-hidroxiciclohexilo, 4-metoxibencilo, 3-(3-hidroxifenoxi)propilo, 3-(3-acetamidofenoxi)propilo, 3-(4-*N*,*N*-dimetilaminocarbonilmetilfenoxi) propilo, 3-(3-carboximetilfenoxi)propilo, 3-(3-metoxicarbonilmetilfenoxi) propilo, 3-(3-metoxicarbonilfenoxi)propilo, 3-(4-carboximetilfenoxi) propilo, 3-(4-metoxicarbonilmetilfenoxi)propilo, 3-(3-acetilaminofenoxi) propilo, 3-(4-hidroxifenilcarboxi)propilo, 3-(4-carboxifenoxi)propilo, 1-(2-nitriloetil)piperidin-4-ilo, isopropilo, etilo, 2,2-dimetilpropilo, *terc*-butilo, 2-(2-metoxietoxi)etilo, 2-hidroxietilo, 2,2,2-trifluoroetilo, metil etanoilglicinato, 2,3-dihidro-1,4-benzodioxin-6-ilmetilo, 1,3,5-trimetil-1H-pirazol-4-ilmetilo, 3-(3,5-dimetil-1H-pirazol-1-il)propilo, 2-(pirrolidin-3-iltio)etilo, 2-[1-(*terc*-butoxicarbonil)pirrolidin-3-il]etilo, 2-[1-(*terc*-butoxicarbonil)pirrolidin-3-il]etilo, 2-{[1-(*terc*-butoxicarbonil) pirrolidin-3-il]tio}etilo, 2-piridin-2-iletilo, 2-{[3-cloro-5-(trifluorometil) piridin-2-il] amino}etilo, 2-{[5-(trifluorometil)piridin-2-il]oxi}etilo, 3-(piridin-2-iloxi) propilo, 1-(*terc*-butoxicarbonil)piperidin-4-ilo, 1-acetilpiperidin-4-ilo, piperidin-4-ilo, 1-metilpiperidin-4-ilo, 1-isobutirilpiperidin-4-ilo, 1-piridin-2-ilpiperidin-4-ilo, 1-(5-fluoropiridin-2-il)piperidin-4-ilo, 1-(5-cloropiridin-2-il)piperidin-4-ilo, 1-(5-metilpiridin-2-il)piperidin-4-ilo, 1-[4-(trifluorometil)piridin-2-il]piperidin-4-ilo, 1-[5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 1-(6-cloropiridin-3-il)piperidin-4-ilo, 1-piridazin-3-ilpiperidin-clorofenil)etilo, 3-(3-carboxifenoxi)propilo, 3-[3-(2-metoxi-2-oxoetil)fenoxi]propilo, 3-[4-(2-metoxi-2-oxoetil)fenoxi]propilo, 3-{4-[2-(dimetilamino)-2-oxoetil]fenoxi}propilo, 3-[(4-hidroxibenzoil)oxi]propilo, 2-{2-[(metilsulfonil)oxi]fenoxi}etilo, 2-{4-[(metilsulfonil)oxi]fenoxi}etilo, 2-[2-(metoxicarbonil)fenoxi]etilo, 2-(4-clorofenoxi)etilo, 2-[3-(trifluorometoxi)fenoxi]etilo, 2-{[3-(trifluorometoxi)fenil]tio}etilo, 2-(bencilamino)-2-oxoetilo, 2-{[3-(difluorometoxi)bencil]amino}-2-oxoetil-

4-ilo, 1-(6-cloropiridazin-3-il)piperidin-4-ilo, 1-(6-metoxipiridazin-3-il) piperidin-4-ilo, 1-(4-cianobencil)piperidin-4-ilo, 1-[2-(trifluorometil) benzoil]piperidin-4-ilo, 1-[3-(metoxicarbonil)bencil]piperidin-4-ilo, 1-bencilpiperidin-4-ilo, 1-benzoilpiperidin-4-ilo, 1-(fenilacetil)piperidin-4-ilo, 1-(4-cianobenzoil)piperidin-4-ilo, 1-(3,4-difluorobenzoil)piperidin-4-ilo, 1-(2-feniletil)piperidin-4-ilo, 1-(2-feniletil)piperidin-4-ilo, 1-bencilpirrolidin-3-ilo, 4-{[4-(trifluorometil)fenil]tio}ciclohexilo, 1-[(5-metilisoxazol-3-il)metil]piperidin-4-ilo, 1-(2-cloro-6-metilisonicotinoil)piperidin-4-ilo, 1-[(2-cloropiridin-3-il)carbonil]piperidin-4-ilo, 2-{4-[(metilsulfonil)oxi] fenil}etilo, 2-[4-(aminosulfonil)fenil]etilo, 2-(4-cianofenil)etilo, 2-(3-cianofenil)etilo, 2-[2-(trifluorometoxi)fenil]etilo o 2-[3-(trifluorometoxi)fenil]etilo.

De acuerdo con un aspecto adicional de la invención, R^1 y R^3 son los mismos que para cualquiera de las incorporaciones 1 a 16, y R^2 es fenilo no sustituido.

De acuerdo con un aspecto adicional de la invención, R^1 y R^3 son los mismos que para cualesquiera reivindicaciones, aspectos o incorporaciones anteriores o sucesivas, y R^2 es fenilo no sustituido.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la primera incorporación de la invención, y R^3 es el mismo que para la primera incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la primera incorporación de la invención, y R^3 es el mismo que para la primera incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o

Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad de que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición meta y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición orto por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la segunda incorporación de la invención, y R^3 es el mismo que para la segunda incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la segunda incorporación de la invención, y R^3 es el mismo que para la segunda incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en

la posición meta y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R , C(O)R , o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la tercera incorporación de la invención, y R^3 es el mismo que para la tercera incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la tercera incorporación de la invención, y R^3 es el mismo que para la tercera incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad que cuando R^1 es C_1- C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición meta y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la cuarta incorporación de la invención, y R^3 es el mismo que para la cuarta incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la cuarta incorporación de la invención, y R^3 es el mismo que para la cuarta incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o para por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la sexta incorporación de la invención, y R^3 es el mismo que para la sexta incorporación de la invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la séptima incorporación de la invención, y R^3 es el mismo que para la séptima incorporación de la invención, excepto que E no se sustituye por Q,

QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la séptima incorporación de la invención, y R^3 es el mismo que para la séptima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o para por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la novena incorporación de la invención, y R^3 es el mismo que para la novena incorporación de la invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima incorporación de la invención, y R^3 es el mismo que para la décima incorporación de la invención, excepto que E no se

sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima incorporación de la invención, y R^3 es el mismo que para la décima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima segunda incorporación de la invención, y R^3 es el mismo que para la décima segunda incorporación de la invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima tercera incorporación de la invención, y R^3 es el mismo que para la décima tercera incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^2Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima tercera incorporación de la invención, y R^3 es el

mismo que para la décima tercera incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima quinta incorporación de la invención, y R^3 es el mismo que para la décima quinta incorporación de la invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima sexta incorporación de la invención, y R^3 es el mismo que para la décima sexta incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^2Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima sexta incorporación de la invención, y R^3 es el mismo que para la décima sexta incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye

opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la primera incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la primera incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la segunda incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la segunda incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la tercera incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la tercera incorporación de la invención, excepto que se excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la cuarta incorporación de la invención, excepto que se

excluye MP; Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la sexta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la sexta incorporación de la invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la séptima incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la séptima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la novena incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la novena incorporación de la invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la décima incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la décima segunda incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima segunda incorporación de la

invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la décima tercera incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima tercera incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la décima quinta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima quinta incorporación de la invención, excepto que se excluye MP; y Het^3, A y Het^5 no se sustituyen por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la décima sexta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima sexta incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1, Het^1Z, R o Het^2Z.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la primera incorporación de la invención, y R^3 es el mismo que para la primera incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la primera incorporación de la invención, y R^3 es el mismo que para la primera incorporación de la invención, excepto que se excluye

MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la segunda incorporación de la invención, y R^3 es el mismo que para la segunda incorporación de la invención, excepto que se excluye MP, Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la segunda incorporación de la invención, y R^3 es el mismo que para la segunda incorporación de la invención, excepto que se excluye MP, Het^5 no se sustituye por Q, QT, Het^1, Het^2T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1

o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la tercera incorporación de la invención, y R^3 es el mismo que para la tercera incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la tercera incorporación de la invención, y R^3 es el mismo que para la tercera incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo,

que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la cuarta incorporación de la invención, y R^3 es el mismo que para la cuarta incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la cuarta incorporación de la invención, y R^3 es el mismo que para la cuarta incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la sexta incorporación de la invención, y R^3 es el mismo que para la sexta incorporación de la invención, excepto que se excluye

MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; y Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la séptima incorporación de la invención, y R^3 es el mismo que para la séptima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la séptima incorporación de la invención, y R^3 es el mismo que para la séptima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la novena incorporación de la invención, y R^3 es el mismo que para la novena incorporación de la invención, excepto que se excluye

MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; y Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la décima incorporación de la invención, y R^3 es el mismo que para la décima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la décima incorporación de la invención, y R^3 es el mismo que para la décima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima segunda incorporación de la invención, y R^3 es el mismo que para la décima segunda incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; y Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la décima tercera incorporación de la invención, y R^3 es el mismo que para la décima tercera incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la décima tercera incorporación de la invención, y R^3 es el mismo que para la décima tercera incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 y R^2 son los mismos que para la décima quinta incorporación de la invención, y R^3 es el mismo que para la décima quinta incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; y Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la décima sexta incorporación de la invención, y R^3 es el mismo que para la décima sexta incorporación de la invención, excepto que E no se

sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 y R^2 son los mismos que para la décima sexta incorporación de la invención, y R^3 es el mismo que para la décima sexta incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_3-C_4cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición meta y/o para por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición orto por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la primera incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la primera incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; y E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la segunda incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la segunda incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T;

y E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la tercera incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la tercera incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; y E no se sustituye por Q, QZ, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la cuarta incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T; y E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la sexta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la sexta incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la séptima incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la séptima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la novena incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la novena incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la décima incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la décima segunda incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima segunda incorporación de la invención, excepto que se excluye MP; Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto de la invención, R^1 es el mismo que para la décima tercera incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima tercera incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la décima quinta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima quinta incorporación de la invención, excepto que se excluye MP; y Het^5 no se sustituye por Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T; Het^3 y A no se sustituyen por Q, QT, Het^1, Het^1T, RT, Het^2 o Het^2T.

De acuerdo con un aspecto adicional de la invención, R^1 es el mismo que para la décima sexta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es el mismo que para la décima sexta incorporación de la invención, excepto que E no se sustituye por Q, QZ, Het^1, Het^1Z, R, Het^2 o Het^2Z; y Het^4 no se sustituye por Q, QZ, Het^1 o R.

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 representa X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 representa Het^3P en donde Het^3 se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde Het^3 se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 representa AP en donde A se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 representa Het^5P en donde Het^5 se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$,

$OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 representa E, el cual se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$, y E se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 es Het^4 el cual se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye

opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y Het^4 se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención, R^2 es fenilo no sustituido, y R^3 representa Het^4, el cual se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Het^2, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y Het^4 se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Het^2, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes

seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

De acuerdo con un aspecto alternativo de la invención, R^1 es el mismo que para la cuarta incorporación de la invención. R^2 es fenilo no sustituido, y R^3 representa Het^4, el cual se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, RZ, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,
y Het^4 se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, RZ, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Todos los aspectos precedentes pueden utilizarse asimismo con cualesquiera reivindicaciones, aspectos o incorporaciones de la invención ya definidos o por definir más adelante.

De acuerdo con un aspecto alternativo de la invención, R^1 se selecciona de n-butilo, *terc*-butilo o 2-metoxietilo, R^2 es fenilo no sustituido, y R^3 se selecciona de etilo, 2,2,2-trifluoroetilo, isopropilo, *terc*-butilo, 2,2-dimetilpropilo, n-hexilo, 2-hidroxietilo, 2-metoxietilo, 3-hidroxipropilo, 2-(2-metoxietoxi)etilo, 3-(2-metoxietoxi)propilo, metil etanoilglicinato o 2,3-dihidroxipropilo.

De acuerdo con un aspecto alternativo de la invención, R^1 se selecciona de n-butilo, *terc*-butilo, etilo, 2-metoxietilo, R^2 es fenilo no sustituido, y R^3 se selecciona de 2,3-dihidro-1,4-benzodioxin-2-ilmetilo, 2,3-dihidro-1,4-benzodioxin-6-ilmetilo, 2-morfolin-4-iletilo, 2-[1-(*terc*-butoxicarbonil) azetidin-3-il]etilo, 3-morfolin-4-ilpropilo, 3-(3,5-dimetil-1*H*-pirazol-1-il)propilo, 2-(pirrolidin-3-iltio)etilo, 2-{[1-(*terc*-butoxicarbonil)pirrolidin-3-il]tio}etilo o 3-[(1-metilpiperidin-4-il)oxi]-3-oxopropilo.

De acuerdo con un aspecto alternativo de la invención, R^1 se selecciona de etilo, *terc*-butilo, n-butilo, isopropilo, 2-metoxietilo, (3-fluorofenil)etilo, ciclopentilo, bencilo, piridin-2ilmetilo, piridin-3ilmetilo, piridin-4ilmetilo, tetrahidrofuran-2ilmetilo, isobutilo, 4-fluorobencilo, (5-metilisoxazol-3-il)metilo o (metiltio)metilo, R^2 es fenilo no sustituido, y R^3 se selecciona de 4-(difluorometoxi)bencilo, 4-metoxibencilo, 2,2- difeniletilo, 2-feniletilo, 2-{4-[(metilsulfonil)oxi]fenil}etilo, 2-[4-(aminosulfonil)fenil]etilo, 2-(4-cianofenil)etilo, 2-(3-cianofenil)etilo, 2-[2- (trifluorometoxi)fenil]etilo, 2-[3-(trifluorometoxi)fenil]etilo, 2-(2-clorofenil)etilo, 3-[bencil(butil)amino]propilo, 4-fenilbutilo, 3-fenoxipropilo, 3-(2-fluorofenoxi)propilo, 3-(3-fluorofenoxi)propilo, 3-(4-fluorofenoxi)propilo, 3-(2-clorofenoxi)propilo, 3-(3-clorofenoxi)propilo, 3-(4-clorofenoxi) propilo, 3-(2-metoxifenoxi)propilo, 3-(3-metoxifenoxi)propilo, 3-(4-metoxifenoxi)propilo, 3-(3-carboxifenoxi)propilo, 3-(4-carboxifenoxi) propilo, 3-(3-hidroxifenoxi)propilo, 3-[3-(hidroximetil)fenoxi]propilo, 3-[4-(hidroximetil)fenoxi]propilo, 3-[3-(2-metoxi-2-oxoetil)fenoxi]propilo, 3-[4-(2-metoxi-2-oxoetil)fenoxi]propilo, 3-[3-(acetilamino)fenoxi]propilo, 3-[3-

(carboximetil)fenoxi]propilo, 3-[3-(metoxicarbonil)fenoxi]propilo, 3-(4-isopropilfenoxi)propilo, 3-[(1-oxidopiridin-3-il)oxi]propilo, 3-{4-[2-(dimetilamino)-2-oxoetil]fenoxi}propilo, 3-[(4- hidroxibenzoil)oxi]propilo, 2-fenoxietilo, 2-{2-[(metilsulfonil)oxi]fenoxi}etilo, 2-{4-[(metilsulfonil) oxi]fenoxi}etilo, 2-[2-(metoxicarbonil)fenoxi]etilo, 2-(4-clorofenoxi)etilo, 2-[3-(trifluorometoxi)fenoxi]etilo, 4-fenoxibutilo, 2-{[3-(trifluorometoxi) fenil]tio}etilo, 3-(feniltio)propilo, 2-(bencilamino)-2-oxoetilo, 2-{[3-(difluorometoxi)bencil]amino}-2-oxoetilo, 2-(3,4-dimetoxifenil)etilo, 2-(3-cloro-4-metoxifenil)etilo, 2-(4-hidroxi-3,5-dimetoxifenil)etilo, 2-(4-metoxifenoxi)-2-oxoetilo, 2-[(4-metoxibencil)oxi]-2-oxoetilo, 2-(2-mesitiletoxi)-2-oxoetilo, 2-(2-mesitil-1-metiletoxi)-2-oxoetilo, 3-oxo-3-fenoxipropilo, 3-oxo-3-[4-(trifluorometoxi)fenoxi]propilo, 2-{[(2,6-dimetilfenil)acetil]oxi}etilo o 4-(2,6-dimetilfenoxi)-4-oxobutilo.

De acuerdo con un aspecto alternativo de la invención, R^1 se selecciona de *terc*-butilo, etilo o isopropilo, R^2 es fenilo no sustituido, y R^3 se selecciona de 2-(1*H*-imidazol-4-il)etilo, 2-piridin-2-iletilo, 2-{[3-cloro-5-(trifluorometil)piridin-2-il]amino}etilo, 2-{[5-(trifluorometil)piridin-2-il]oxi}etilo, 3-(piridin-2-iloxi)propilo, 3-(piridin-3-iloxi)propilo, 3-(piridin-4-iloxi)propilo, (1,3,5-trimetil-1*H*-pirazol-4-il)metilo, 3-[(1-oxidopiridin-3-il) oxi]propilo o (5-metilisoxazol-3-il)metilo, 2-(2-aminopiridin-4-il)etilo, 2-piridin-4-iletilo, 2-piridin-3-iletilo, 2-(3,5-dimetilisoxazol-4-il)etilo o 2-(3,5-dimetil-1*H*-pirazol-4-il)etilo.

De acuerdo con un aspecto alternativo de la invención, R^1 se selecciona de n-butilo, isopropilo o 2-metoximetilo, R^2 es fenilo no sustituido, y R^3 se selecciona de *trans*-4-hidroxiciclohexilo, *cis*-4-hidroxiciclohexilo, 4-hidroxiciclohexilo, 4,4-difluorociclohexilo o 2,3-dihidro-1*H*-inden-2-ilo.

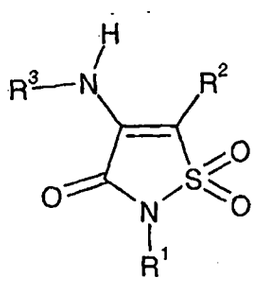
De acuerdo con un aspecto alternativo de la invención, R^1 se selecciona de *terc*-butilo, isopropilo o 2-metoxietilo, R^2 es fenilo no sustituido, y R^3 se selecciona de 1-(2-cianoetil)piperidin-4-ilo, 1-(*terc*-butoxicarbonil)

piperidin-4-ilo, 1-acetilpiperidin-4-ilo, piperidin-4-ilo, 1-metilpiperidin-4-ilo, 1-isobutirilpiperidin-4-ilo o tetrahidro-2*H*-piran-4-ilo.

De acuerdo con un aspecto alternativo de la invención, R^1 se selecciona de isopropilo o *terc*-butilo, R^2 es fenilo no sustituido, y R^3 se selecciona de 1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 1-piridin-2-ilpiperidin-4-ilo, 1-(5-fluoropiridin-2-il)piperidin-4-ilo, 1-(5- cloropiridin-2-il)piperidin-4-ilo, 1-(5-metilpiridin-2-il)piperidin-4-ilo, 1-[4-(trifluorometil) piridin-2-il]piperidin-4-ilo, 1-[5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 1-(6-cloropiridin-3-il)piperidin-4-ilo, 1-piridazin-3-ilpiperidin-4-ilo, 1-(6-cloropiridazin-3-il)piperidin-4-ilo, 1-(6-metoxipiridazin-3-il)piperidin-4-ilo, 1-[4-(trifluorometil)pirimidin-2-il] piperidin-4-ilo, 1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-ilo o 1-piridin-2-ilazetidin-3-ilo.

Todos los aspectos precedentes pueden utilizarse asimismo con cualesquiera reivindicaciones, aspectos o incorporaciones de la invención ya definidos o por definir más adelante.

En una incorporación alternativa se provee un compuesto de la fórmula general (I), o su sal farmacéuticamente aceptable, en donde R^1 y R^3 son como se definen en cualquier reivindicación, aspecto o incorporación de la invención ya indicada o por indicar, y en donde R^2 es fenilo no sustituido.



fórmula (I)

En otra incorporación alternativa se provee un compuesto de la fórmula general I, o su sal farmacéuticamente aceptable, en donde R^1 y R^3 son como se definen en cualquier reivindicación, aspecto o incorporación de la invención ya indicada o por indicar, y en donde R^2 es fenilo, el cual se

sustituye opcionalmente en la posición orto por cualquiera de los sustituyentes apropiados ya descritos o por describir más adelante.

En otra incorporación alternativa se provee un compuesto de la fórmula general I, o su sal farmacéuticamente aceptable, en donde R^1 y R^3 son como se definen en cualquier reivindicación, aspecto o incorporación de la invención ya indicada o por indicar, y en donde R^2 es fenilo, el cual se sustituye opcionalmente por halógeno (F, Cl, Br, I).

Las anteriores incorporaciones pueden combinarse con cualquier otra incorporación, aspecto o reivindicación de la invención ya descritos o por describir más adelante más adelante.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la primera incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la segunda

incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la tercera incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la cuarta incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br),

OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la quinta incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la séptima incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$,

$NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la octava incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la décima incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la undécima incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la décima tercera incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la décima cuarta incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F; R^3 es C_1-C_4alquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la

posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general I en donde R^1, R^2 y R^3 se definen como para la décima sexta incorporación de la invención, con la salvedad que cuando R^1 es C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de F, R^3 es C_3-C_6cicloalquilo, entonces R^2 es fenilo, el cual se sustituye opcionalmente en la posición *meta* y/o *para* por halógeno (F, Cl, Br, I) y/o se sustituye opcionalmente en la posición *orto* por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, o $C(O)R^b$.

Las anteriores incorporaciones pueden combinarse con cualquier otra incorporación, aspecto o reivindicación de la invención ya descritos o por describir más adelante más adelante.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general (I) en donde R^1, R^2, y R^3 son como se definen para cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante, con la salvedad que cuando R^1 es C_1-C_4alquilo, sustituido opcionalmente por uno o más F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 no es fenilo, sustituido en la posición *para* por un C_1alquilo, que lleva un sustituyente seleccionado de:

NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ o $NR^aC(O)NR^aR^a$, y un sustituyente seleccionado de: $C(O)R^b$, $C(O)OR^a$ o $C(O)NR^aR^a$; y R^2 no es fenilo, sustituido en la posición para por un por una cadena C_2-C_4alquilo recto o ramificado, en la cual el átomo de carbono terminal (es decir, el carbono no conectado al fenilo) lleva un sustituyente seleccionado de: NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ o $NR^aC(O)NR^aR^a$, y un sustituyente seleccionado de: $C(O)R^b$, $C(O)OR^a$ o $C(O)NR^aR^a$; en donde R^a y R^b son como se definen para cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante.

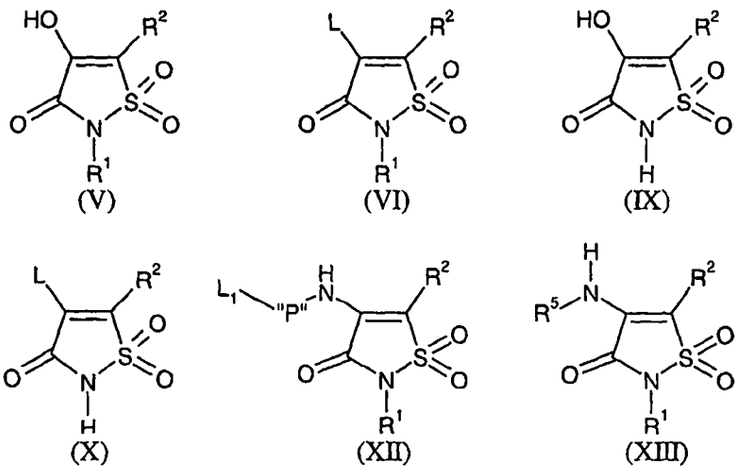
En una incorporación alternativa de la invención se provee un compuesto de la fórmula general (I) en donde R^1, R^2, y R^3 son como se definen para cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante, con la salvedad que cuando R^1 es C_1-C_4alquilo, sustituido opcionalmente por uno o más F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 no es fenilo, sustituido en la posición *para* por un C_1alquilo, que lleva un sustituyente seleccionado de: NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ o $NR^aC(O)NR^aR^a$, y un sustituyente seleccionado de: $C(O)R^b$, $C(O)OR^a$ o $C(O)NR^aR^a$; y R^2 no es fenilo, sustituido en la posición para por una cadena C_2-C_4alquilo recto o ramificado, en la cual el átomo de carbono terminal (es decir, el carbono no conectado al fenilo) lleva un sustituyente seleccionado de: NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$, $NR^aC(O)OR^b$ o $NR^aC(O)NR^aR^a$, y un sustituyente seleccionado de: $C(O)R^b$, $C(O)OR^a$ o $C(O)NR^aR^a$; en donde R^a y R^b son como se definen para cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante, y R^2 no es fenilo, el cual se sustituye posteriormente en las posiciones *orto* o *meta* por H, halógeno, C_1-C_4alquilo, OH, OR^b, SR^b, NO_2, CN, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$ $C(O)OR^a$, NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$ o $NR^aC(O)NR^aR^a$.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general (I) en donde R^1, R^2, y R^3 son como se definen para

cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante, con la salvedad que cuando R^1 es C_1-C_4alquilo, sustituido opcionalmente por uno o más F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 no es fenilo sustituido en la posición *meta* por NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)OR^a$, $C(O)NR^aR^a$ o $OC(O)R^b$; en donde R^a y R^b son como se definen para cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante, con la salvedad que cuando R^2 es fenilo sustituido en la posición *meta* por $C(O)OR^a$, entonces R^a puede ser H.

En una incorporación alternativa de la invención se provee un compuesto de la fórmula general (I) en donde R^1, R^2, y R^3 son como se definen para cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante, con la salvedad que cuando R^1 es C_1-C_4alquilo sustituido opcionalmente por uno o más F, o R^1 es C_3-C_6cicloalquilo; R^3 es C_1-C_4alquilo o C_3-C_6cicloalquilo, entonces R^2 no es fenilo sustituido en una de las posiciones meta por NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)OR^a$, $C(O)NR^aR^a$ o $OC(O)R^b$; en donde R^a y R^b son como se definen para cualquier aspecto, reivindicación o incorporación ya mencionados o por mencionar más adelante, con la salvedad que cuando R^2 es fenilo sustituido en la posición *meta* por $C(O)OR^a$,entonces R^a puede ser H, y R^2 no es fenilo, el cual se sustituye posteriormente en la posición orto, para u otra meta por H, halógeno, C_1-C_4alquilo, OH, OR^b, SR^b, NO_2, CN, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $C(O)OR^a$, NR^aR^a, $NR^aSO_2R^b$, $NR^aC(O)R^b$ o $NR^aC(O)NR^aR^a$.

En un aspecto adicional de la invención se provee un compuesto de la fórmula general (V), (VI), (IX), (X), (XII) o (XIII)



o su sal farmacéuticamente aceptable,

en donde R^1 es como se define para cualesquiera aspectos, incorporaciones o reivindicaciones ya mencionadas o por mencionar más adelante, R^2 es como se define para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante, L es un grupo saliente apropiado tal como Cl, Br, I, p-toluenosulfonato, metanosulfonato o trifluorometanosulfonato, "P" es como se define para P en cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante, L_1 es OH, NH_2, SH o un grupo saliente apropiado tal como Cl, Br, I, p-toluenosulfonato, metanosulfonato o trifluorometanosulfonato, y R^5 es Het^4 o E en donde Het^4 y E son como se definen para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante, con la salvedad de que se excluyen los siguientes compuestos: 1,1-dióxido de 4-hidroxi-5-fenilisotiazol-3(2*H*)-ona, 1,1-dióxido de 5-(4-aminofenil)-4-hidroxi-2-metilisotiazol-3(2*H*)-ona, 1,1-dióxido de 4-hidroxi-2-metil-5-(4-nitrofenil)isotiazol-3(2*H*)-ona, 1,1-dióxido de 4-hidroxi-2-metil-5-fenilisotiazol-3(2*H*)-ona, 1,1-dióxido de 5-(3,4-diclorofenil)-4-hidroxiisotiazol-3(2*H*)-ona, 1,1-dióxido de 2-bencil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona, y 1,1-dióxido de 4-hidroxi-2-(4-metilfenil)-5-

fenilisotiazol-3(2*H*)-ona. Se entenderá que pueden usarse grupos protectores cuando L_1 es OH, NH_2 ó SH.

Ciertos compuestos de la presente invención pueden existir como tautómeros o estereoisómeros (por ejemplo, racemato, enantiómero, diastereómero o E- o Z-isómero). Hay que entender que la presente invención abarca la totalidad de tales tautómeros o estereoisómeros.

Ciertos compuestos de la presente invención pueden existir como solvatos o hidratos. Hay que entender que la presente invención incluye la totalidad de tales solvatos o hidratos.

Los compuestos de la presente invención pueden contener igualmente proporciones no naturales de isótopos atómicos en uno o más de los átomos que constituyen tales compuestos. Por ejemplo, los compuestos pueden radiomarcarse con isótopos radioactivos, tales como por ejemplo tritio (^3H), yodo 125 (^{125}I) o carbono 14 (^{14}C). Todas las variaciones isotópicas de los compuestos de la presente invención, radioactivos o no, tienen por objeto quedar incluidos dentro del ámbito de la presente invención.

Una sal farmacéuticamente aceptable de un compuesto de la invención es, por ejemplo, una sal de adición de ácido de un compuesto de la invención que es suficientemente básica, por ejemplo, una sal de adición de ácido con, por ejemplo, un ácido orgánico o inorgánico, por ejemplo ácido clorhídrico, bromhídrico, nítrico, metanosulfónico, sulfúrico, fosfórico, trifluoroacético, *terc*-toluenosulfónico, 2-mesitilen sulfónico, cítrico, acético, tartárico, fumárico, láctico, succínico, málico, malónico, maleico, 1,2-etanodisulfónico, adípico, aspártico, bencenosulfónico, benzoico, etanosulfónico o nicotínico. Además, una sal farmacéuticamente aceptable de un compuesto de la invención, es, por ejemplo, una sal de adición de ácido de un compuesto de la invención, que es suficientemente ácida, por ejemplo, una sal de metal, por ejemplo, una sal de sodio, potasio, calcio,

magnesio, zinc o aluminio, una sal de amonio, una sal con una base orgánica que suministra un catión fisiológicamente aceptable, la cual incluye hidróxidos de amonio cuaternario, por ejemplo metilamina, etilamina, dietilamina, trimetilamina, *terc*-butilamina, trietilamina, dibencilamina, N,N-dibenciletilamina, ciclohexiletilamina, tris-(2-hidroxietil)amina, hidroxietildietilamina, (1R, 2S)-2-hidroxiinden-1-amina, morfolina, N-metilpiperidina, N-etilpiperidina, piperazina, metilpiperazina, adamantilamina, hidróxido de colina, hidróxido de tetrabutilamonio, hidróxido de tris-(hidroximetil)metilamina, l-arginina, N-metil D-glucamina, lisina o arginina.

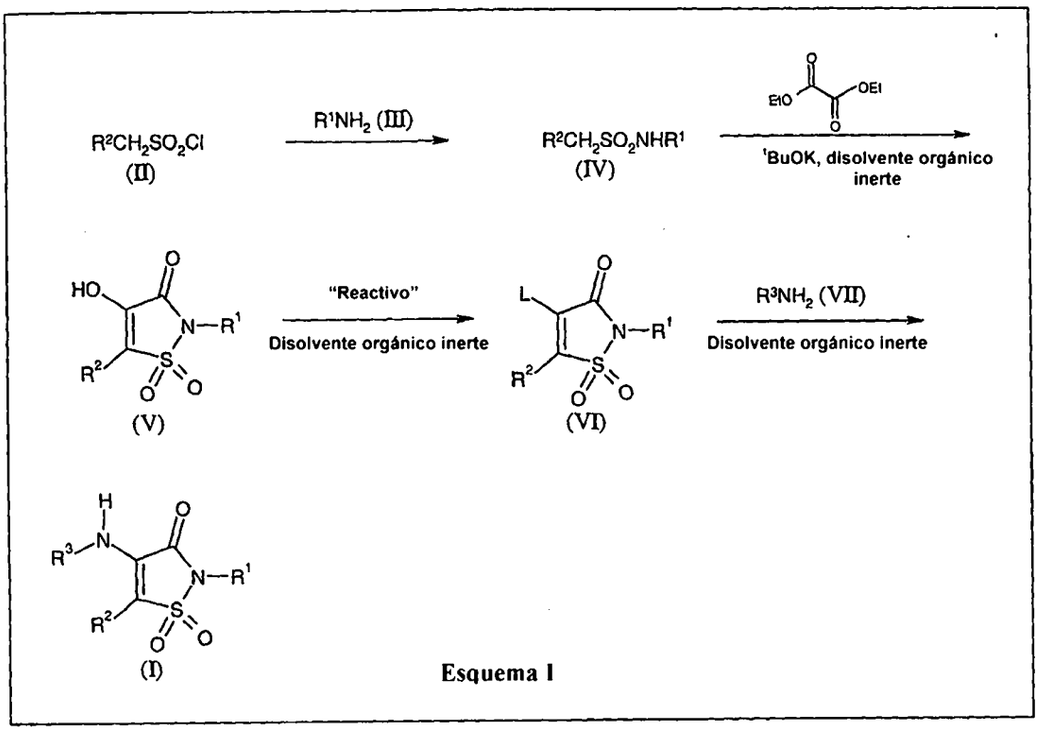
El compuesto de fórmula (I), u otros compuestos divulgados en esta solicitud, puede administrarse en la forma de un profármaco, que se descompone en el cuerpo animal o humano para producir un compuesto de la fórmula (I). Ejemplos de profármacos incluyen ésteres hidrolizables *in vivo* y amidas hidrolizables *in vivo* de un compuesto de la fórmula (I).

Métodos de preparación

Los compuestos de la invención pueden prepararse como se describe en los siguientes Esquemas. No obstante, la invención no se limita a estos métodos. Los compuestos pueden prepararse asimismo como se describe para compuestos relacionados estructuralmente en el arte previo. Las reacciones pueden llevarse a cabo de acuerdo con procedimientos estándar, o como se describe en la sección experimental.

En los Esquemas que sigue el término "reactivo" significa un reactivo que puede transformar un grupo hidroxi en un grupo saliente L. Ejemplos de tales grupos salientes son por ejemplo Cl, Br, I, metanosulfonato (OMs), p-toluensulfonato o trifluorometanosulfonato (OTf). Además, en todos los Esquemas siguientes R^1, R^2 y R^3 son como se definen para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o que se indicarán más adelante.

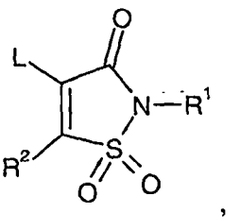
Esquemas I - IX ilustran diferentes procesos para sintetizar compuestos de fórmula (I).



Esquema I

Esquema I describe un método de preparación de compuestos de acuerdo con fórmula (I), en donde R^1, R^2 y R^3 son como se definen para cualesquiera aspectos o incorporaciones ya mencionadas o que se mencionarán más adelante, y L es un grupo saliente tal como por ejemplo Cl, Br, I, p-toluensulfonato, metanosulfonato o trifluorometanosulfonato, método que comprende los siguientes pasos:

a) Un proceso para la preparación de un compuesto de acuerdo con fórmula (I) que comprende el paso de hacer reaccionar un compuesto de fórmula (VI)



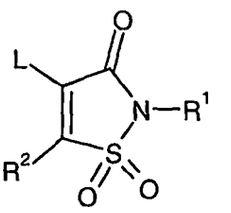
(VI)

(VI) con un compuesto de fórmula (VII)

R^3NH_2 (VII),

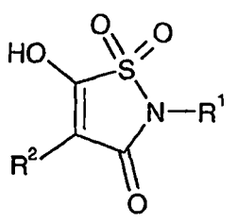
opcionalmente en la presencia de un disolvente orgánico inerte tal como dimetilformamida.

b) Un proceso para la preparación de un compuesto de acuerdo con la fórmula (VI)



(VI)

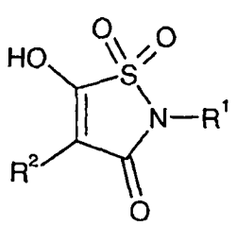
que comprende el paso de hacer reaccionar un compuesto de fórmula (V)



(V)

con un reactivo que puede transformar el grupo hidroxi en el compuesto de fórmula (V) en un grupo saliente L, opcionalmente en la presencia de un disolvente orgánico inerte.

c) Un proceso para la preparación de un compuesto de acuerdo con la fórmula (V)



(V)

que comprende el paso de hacer reaccionar un compuesto de fórmula (IV)

$$R^2CH_2SO_2NHR^1 \text{ (IV)}$$

con oxalato de dietilo, o su equivalente apropiado, en la presencia de una tal como por ejemplo *terc*-butóxido de potasio, opcionalmente en la presencia de un disolvente orgánico tal como THF.

d) Un proceso para la preparación de un compuesto de acuerdo con la fórmula (IV)

$$R^2CH_2SO_2NHR^1 \quad (IV),$$

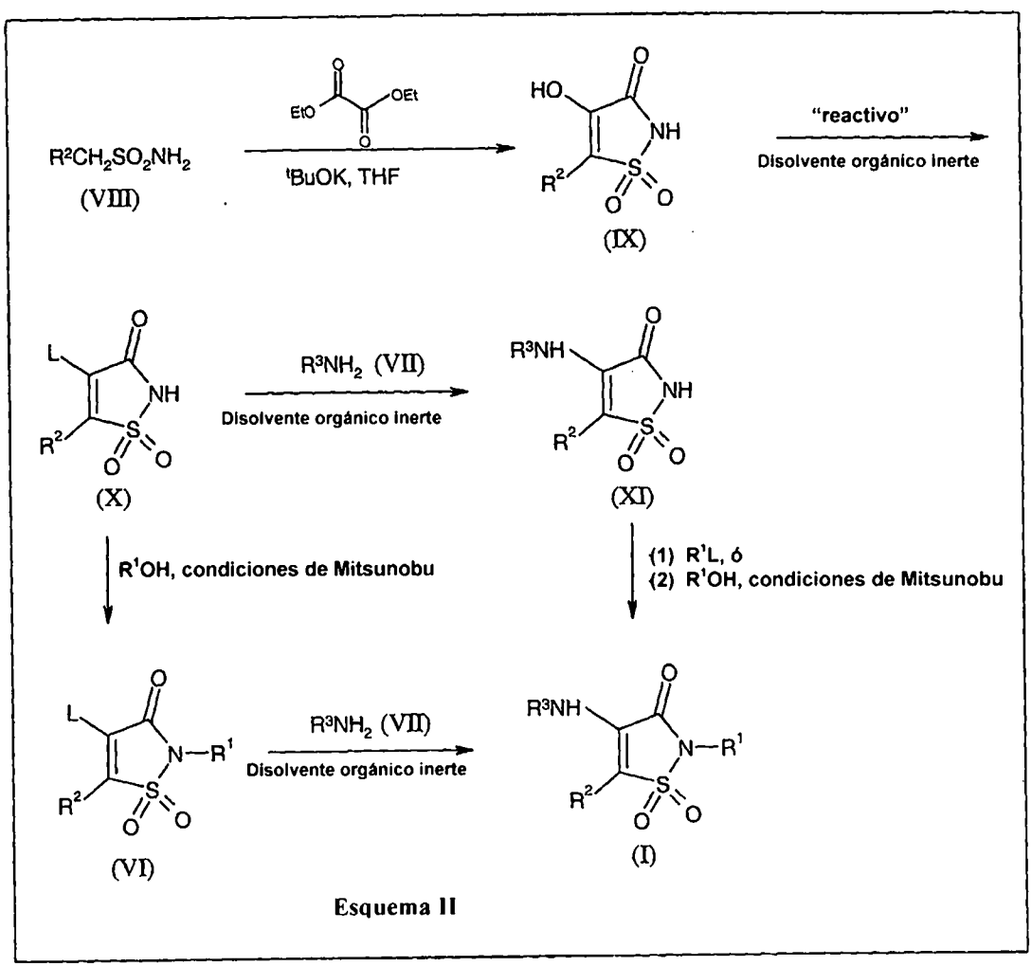
que comprende el paso de hacer reaccionar un compuesto de fórmula (II)

$$R^2CH_2SO_2Cl \ (II)$$

con un compuesto de fórmula (III)

$$R^1NH_2 \ (III),$$

opcionalmente en la presencia de una base y un disolvente orgánico inerte.

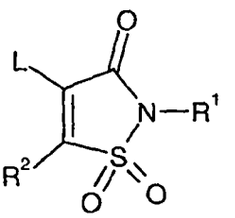


Esquema II

Esquema II describe un método de preparación de compuestos de acuerdo con la fórmula (I), en donde R^1, R^2 y R^3 son como se definen para cualesquiera aspectos o incorporaciones ya mencionados o indicados más adelante, y L es un grupo saliente tal como por ejemplo Cl, Br, I, p-toluensulfonato, metanosulfonato o trifluorometanosulfonato, que comprende los siguientes pasos:

a) Un proceso para la preparación de un compuesto de acuerdo con la fórmula (I) que comprende el paso de hacer reaccionar

(i) un compuesto de fórmula (VI)

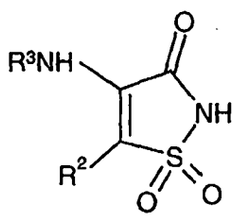


(VI)

con un compuesto de fórmula (VII)

$$R^3NH_2 \text{ (VII)},$$

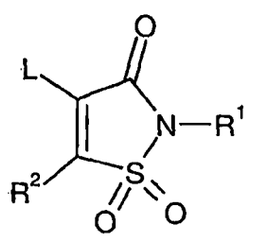
opcionalmente en la presencia de un disolvente orgánico inerte tal como dimetilformamida; o (ii) un compuesto de fórmula (XI)



(XI)

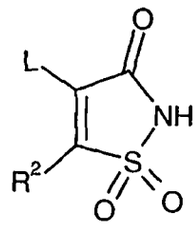
o bien con R^1OH usando condiciones de Mitsunobu o bien con un agente alquilante tal como R^1L.

b) Un proceso para la preparación de un compuesto de acuerdo con la fórmula (VI)



(VI)

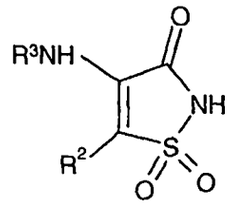
que comprende el paso de hacer reaccionar un compuesto de fórmula (X)



(X)

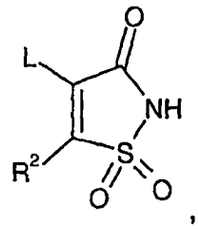
con R^1OH usando condiciones de Mitsunobu.

c) Un proceso para la preparación de un compuesto de acuerdo con la fórmula (XI)



(XI)

que comprende el paso de hacer reaccionar un compuesto de fórmula (X)



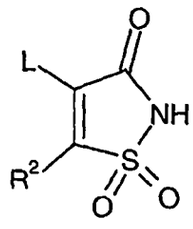
(X)

con un compuesto de fórmula (VII)

$$R^3NH_2 \text{ (VII)},$$

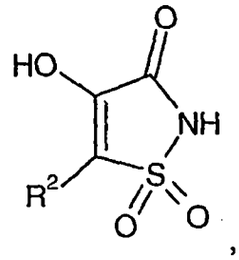
opcionalmente en la presencia de un disolvente orgánico inerte,

d) Un proceso para la preparación de un compuesto de acuerdo con la fórmula (X)



(X)

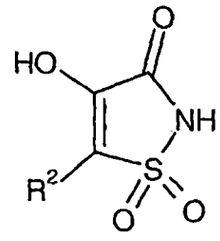
que comprende el paso de hacer reaccionar un compuesto de fórmula (IX)



(IX)

con un reactivo que transforma el grupo hidroxi en el compuesto de fórmula (IX) en un grupo saliente L.

e) Un proceso para la preparación de un compuesto de fórmula (IX)

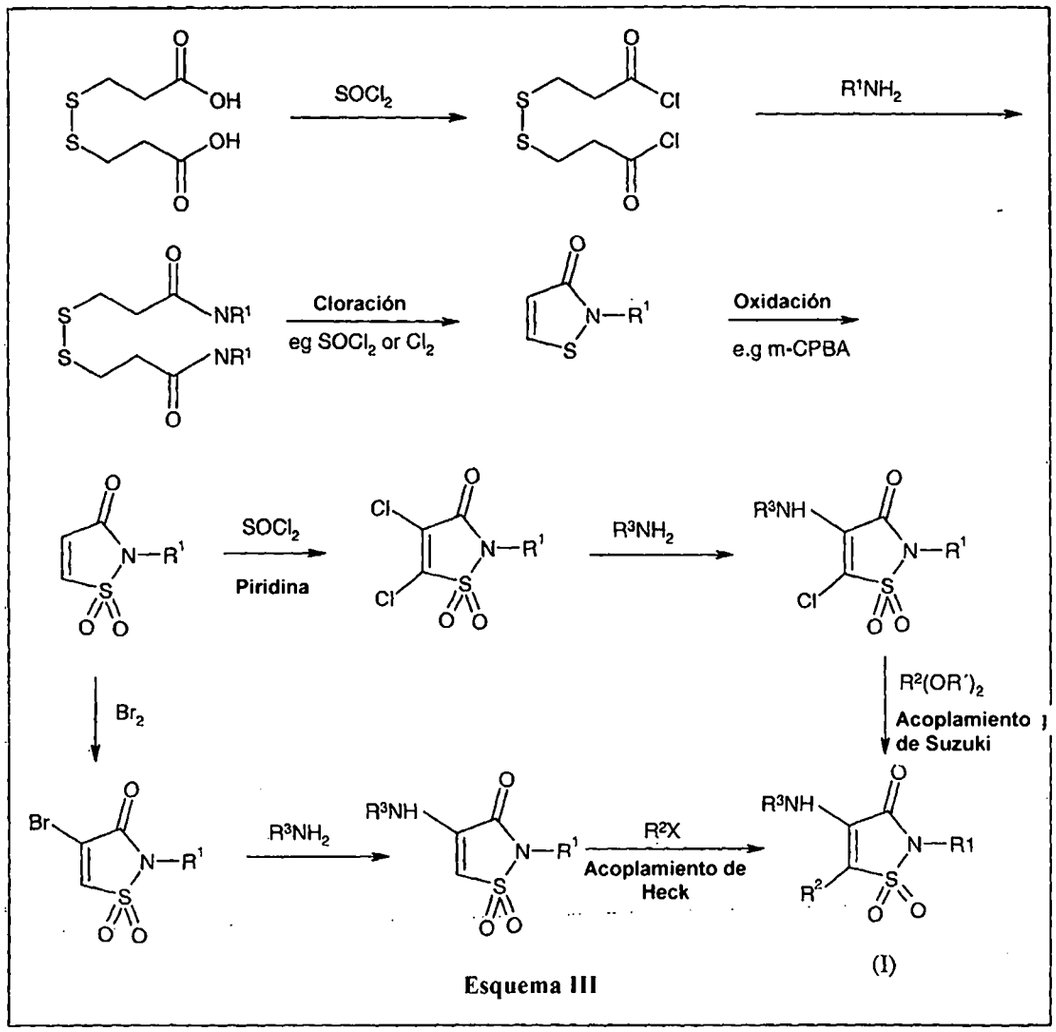


(IX)

que comprende el paso de hacer reaccionar un compuesto de fórmula (VIII)

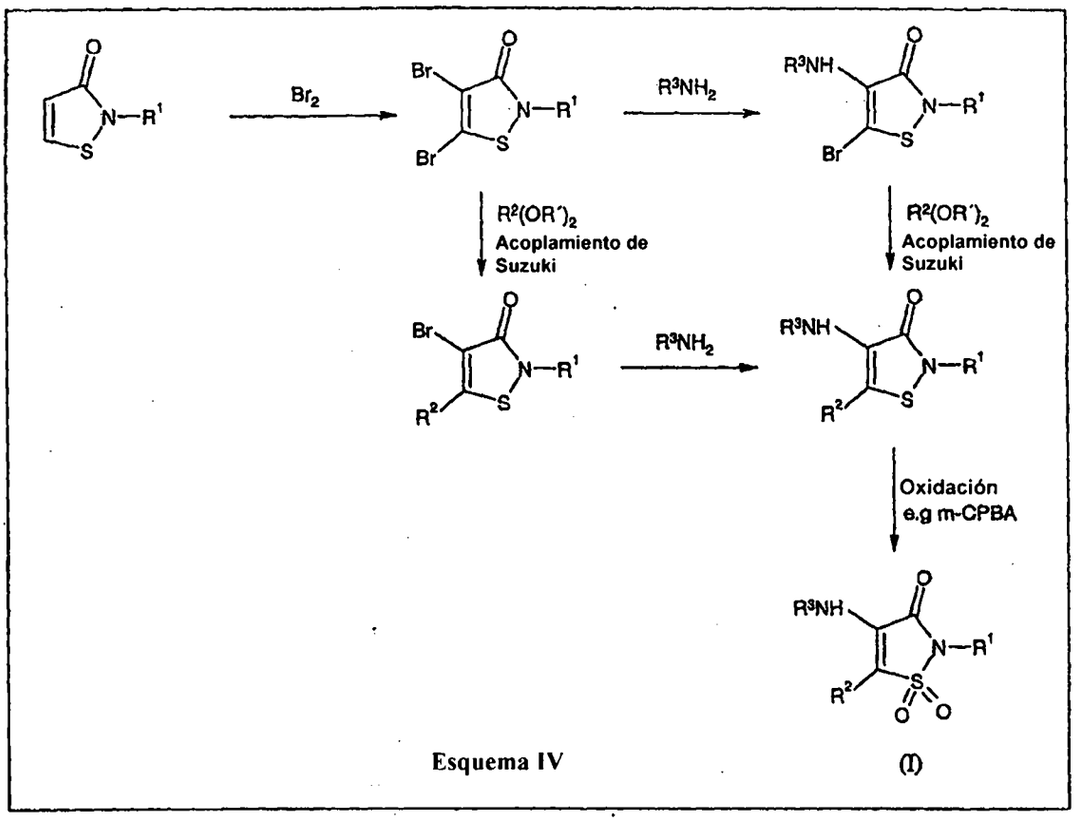
$$R^2CH_2SO_2NH_2 \text{ (VIII)}$$

con oxalato de dietilo, o su equivalente apropiado, en la presencia de una base tal como, por ejemplo *terc*-butóxido de potasio, opcionalmente en la presencia de un disolvente orgánico inerte tal como THF.

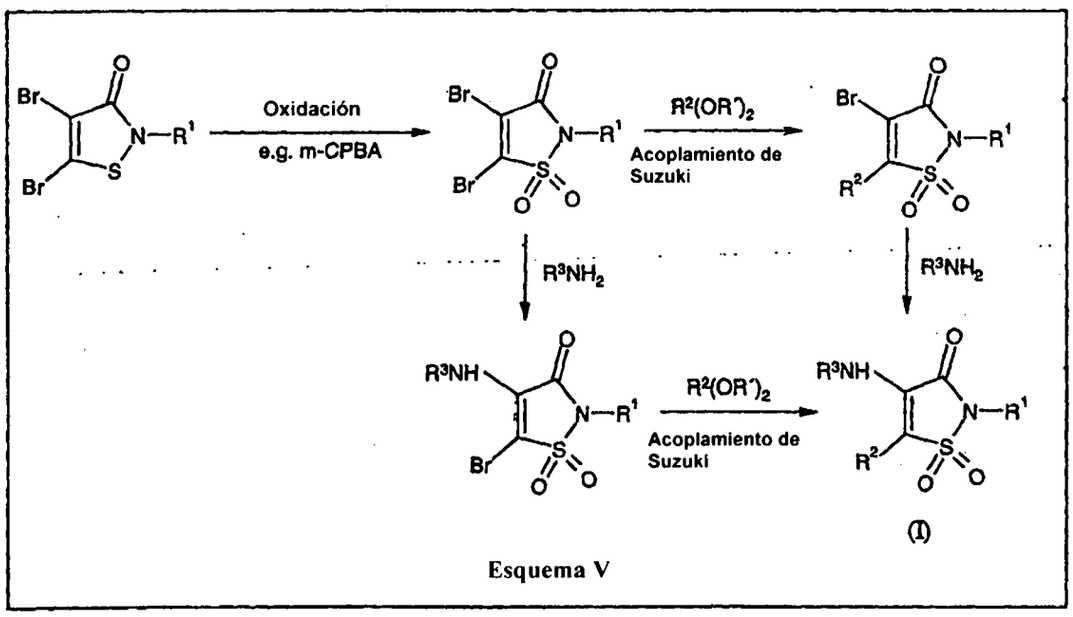


Esquema III

En Esquema III, R^2X es un haluro de arilo, en donde R^2 se define como para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante. Además, en los Esquemas III, IV y V, $R^2(OR')_2$ es un reactivo en donde R^2 se define como para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante y R' es un hidrocarburo.



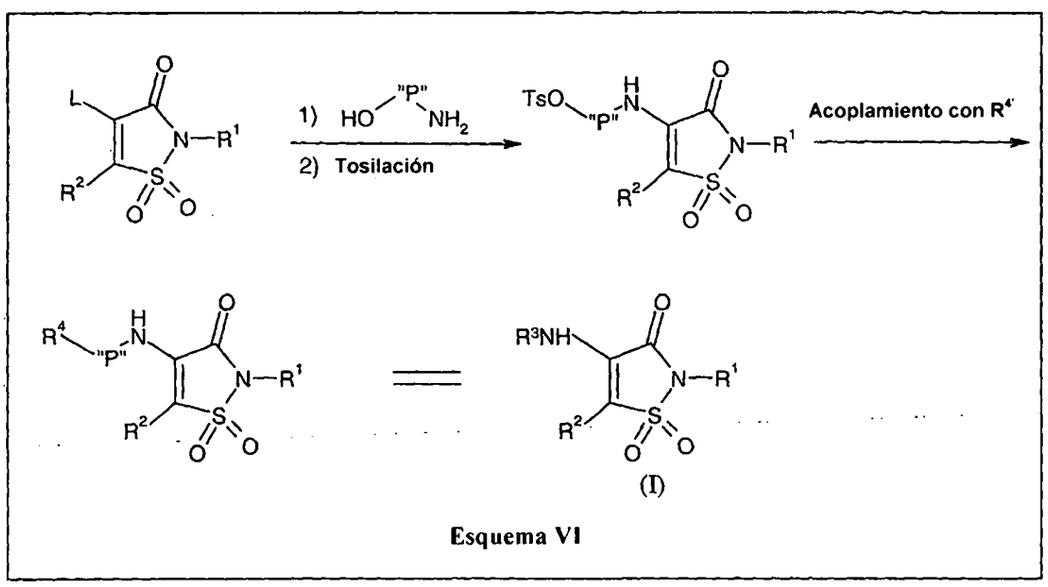
Esquema IV (I)



Esquema V (I)

Esquema VI ilustra además la síntesis de algunos de los compuestos de la invención. En Esquema VI, "P" se define como para P en cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante, $R^{4'}$ es un derivado apropiado de M, Het, A o Het, que se sustituyen opcionalmente por uno o más de los siguientes seleccionados independientemente de: Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T. $R^{4'}$ reactúa con el tosilato para producir un compuesto de fórmula (I). Se

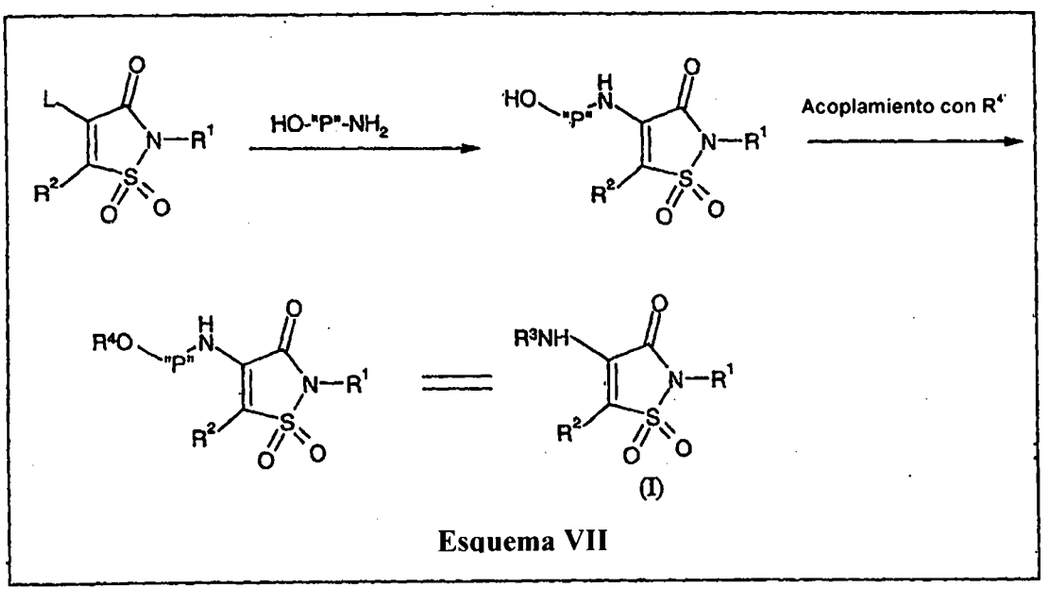
observará que en Esquema VI pueden utilizarse grupos salientes diferentes de tosilatos. Más aún, en Esquema VI, el tosilato, u otro grupo saliente apropiado, puede transformarse en un nucleófilo tal como por ejemplo amino, hidroxi o tio. El acoplamiento con el reactivo $R^{4'}$ se lleva a cabo usando condiciones apropiadas de reacción, conocidas por una persona experta en el arte, y ejemplos de este acoplamiento pueden encontrarse en la parte experimental de esta solicitud. R^4-"P"- NH es igual a R^aNH. R^4 es M, Het^3, A o Het^5, los cuales se sustituyen opcionalmente por uno o más de los siguientes seleccionados independientemente de: Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T. M, Het^3, A, Het^5, Q, T, Het^1, R y Het^2 se definen como para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante.



Esquema VI

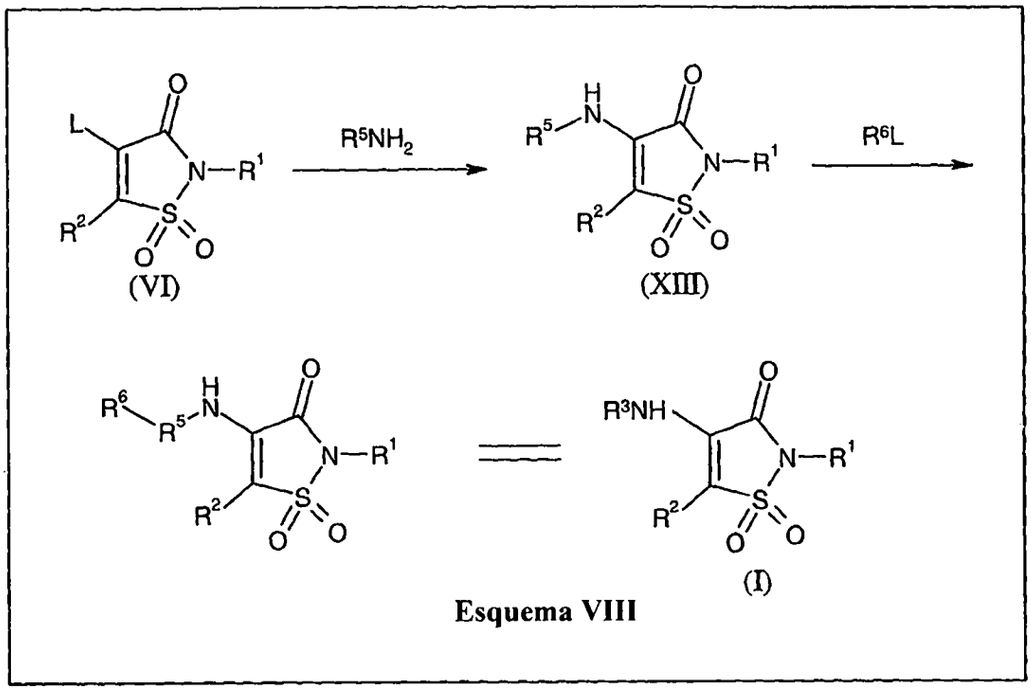
Esquema VII ilustra además la síntesis de algunos de los compuestos de la invención. En Esquema VII, "P" se define como para P en cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante, $R^{4'}$ es un derivado apropiado de M, Het^3, A o Het^5, los cuales se sustituyen opcionalmente por uno o más de los siguientes seleccionados independientemente de: Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T. $R^{4'}$ reacciona con el grupo hidroxi para producir un compuesto de fórmula (I). El acoplamiento con el reactivo $R^{4'}$ se lleva a cabo usando condiciones apropiadas de reacción conocidas por las personas expertas en el arte, y

ejemplos de este acoplamiento pueden encontrarse en la parte experimental de esta solicitud. R^4O-"P"-NH es igual a R^3NH. R^4 es M, Het^3, A o Het^5, los cuales se sustituyen opcionalmente por uno o más de los siguientes seleccionados independientemente de: Q, QT, Het^1, Het^1T, R, RT, Het^2 o Het^2T. M, Het^3, A, Het^5, Q, T, Het^1, R y Het^2 se definen como para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante. Se observa que en el Esquema VII pueden usarse nucleófilos diferentes de hidroxi, tal como por ejemplo tio y amino.



Esquema VII

Esquema VIII ilustra además la síntesis de algunos de los compuestos de la invención. En Esquema VIII, R^5NH_2 es Het^4NH_2 o $E\text{-}NH_2$. Het^4 y E son como se definen para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante. R^6L es un reactivo en el cual R^6 es Q, QZ, Het^1, Het^1Z, R, RZ, Het^2 o Het^2Z, y L es un grupo saliente tal como por ejemplo Cl, Br, I, p-toluenosulfonato, metanosulfonato o trifluorometanosulfonato. Q, Z, Het^1, R, y Het^2 son como se definen para cualesquiera aspectos, incorporaciones o reivindicaciones ya indicadas o señaladas más adelante. R^6-R^5-NH es igual a R^3NH. El acoplamiento con R^6L se lleva a cabo usando condiciones apropiadas de reacción conocidas por una persona experta en el arte, y ejemplos de este acoplamiento pueden encontrarse en la parte experimental de esta solicitud.

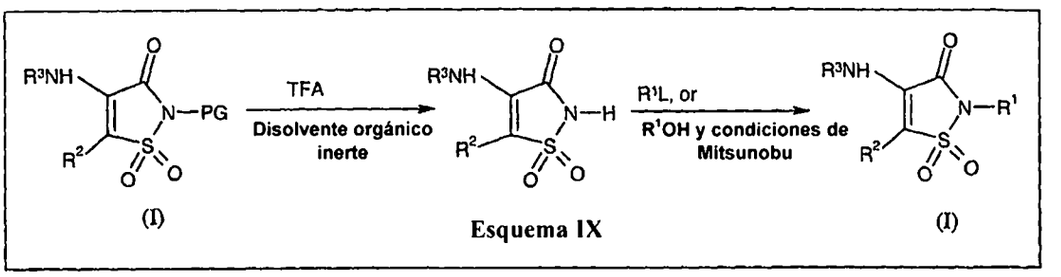


Esquema VIII

La expresión "disolvente orgánico inerte" se refiere a un disolvente que no reacciona con los materiales de partida, reactivos, intermedios o productos en una manera que afecte negativamente el rendimiento del producto deseado. Ejemplos de tales disolventes son, por ejemplo, dimetilformamida, cloruro de metileno y acetonitrilo.

Los pasos de reacción individuales en los Esquemas I - VIII pueden realizarse calentando simultáneamente usando medios convencionales tales como calentando la mezcla de reacción en un baño de aceite, o calentando la mezcla de reacción en un horno microondas.

Además, se entenderá que el grupo R^1 en un compuesto de fórmula (I) puede reemplazarse por otro grupo R^1, por ejemplo, ciclopentilo. Por ejemplo, cuando R^1 es *terc*-butilo, éste puede retirarse mediante desprotección con ácido trifluoroacético, y el compuesto resultante puede hacerse reaccionar posteriormente con un agente alquilante que contiene el nuevo grupo R^1. Esto se ilustra en el Esquema IX, donde PG denota un grupo protector.



Esquema IX

Se entenderá que, en algunas de las reacciones en esta solicitud, puede ser necesario usar un grupo protector para funcionalidades tales como, por ejemplo, grupos hidroxilo, grupos amino y grupos carboxilo. Otros grupos protectores representativos pueden hallarse en T. W. Green and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., Wiley and Sons, Inc., New York (1999), el cual se incorpora por la presente solicitud por referencia en su totalidad.

Se entenderá que el oxalato de dietilo utilizado en los Esquemas ya indicados puede intercambiarse por reactivos equivalentes, tales como, por ejemplo, cloruro de metil oxalilo.

Se entenderá que el *terc*-butóxido de potasio utilizado en los Esquemas ya indicados puede intercambiarse por reactivos equivalentes, tales como, por ejemplo, *terc*-butóxido de litio.

Compuestos de fórmula (II) y (IV) se encuentran disponibles en el comercio o pueden prepararse como se describe en la parte experimental de esta solicitud de patente o por métodos conocidos por aquellas personas expertas en el arte.

Compuestos de fórmula (VII) se encuentran disponibles en el comercio o pueden prepararse como se describe en la parte experimental en esta solicitud de patente o mediante métodos conocidos por las personas expertas en el arte. Además, compuestos de fórmula (VII) pueden

prepararse en una forma análoga a los procedimientos descritos en la parte experimental en esta solicitud de patente.

Se considera que ciertos compuestos de fórmula (V), (VI), (IX), (X), (XII) y (XIII) son novedosos y se reivindican en esta solicitud como intermedios útiles en la preparación de compuestos de fórmula (I). Todos los intermedios se encuentran disponibles en el comercio o pueden prepararse como se describe en la parte experimental en esta solicitud de patente o mediante métodos conocidos por las personas expertas en el arte. Además, los intermedios pueden prepararse en una forma análoga a los procedimientos descritos en la parte experimental en esta solicitud de patente.

Hay que entender que cuando R^1 o R^3 representan óxidos de nitrógeno en compuestos de fórmula (I), éstos se preparan de las minas correspondientes y un agente oxidante tal como ácido metacloroperbenzoico (MCPBA) opcionalmente en la presencia de un disolvente orgánico inerte, tal como diclorometano.

Personas expertas en el arte observarán que, con el fin de obtener compuestos de la invención en una manera alternativa y, en algunas ocasiones, más conveniente, los pasos de los procesos individuales mencionados más arriba en el texto pueden llevarse a cabo en un orden diferente, y/o las reacciones individuales pueden realizarse en una etapa diferente en la ruta general (es decir, pueden efectuarse transformaciones químicas sobre intermedios, diferentes a los asociados más arriba en el texto, con una reacción particular).

Preparaciones farmacéuticas

Los compuestos de la invención se administrarán normalmente por la vía oral, parenteral, intravenosa, intramuscular, subcutánea o en otras vías inyectables, sublingual, rectal, vaginal, transdérmica y/o nasal y/o mediante

inhalación, en la forma de preparaciones farmacéuticas que compren el ingrediente activo o su sal farmacéuticamente aceptable, o su solvato, o un solvato de tal sal, en una presentación farmacéuticamente aceptable. Dependiendo del trastorno y el paciente a tratar y la vía de administración, las composiciones pueden administrarse en dosis variables.

Dosis diarias apropiadas de los compuestos de la invención en el tratamiento terapéutico de humanos son de alrededor de 0.0001-100 mg/kg de peso corporal, preferiblemente 0.01-10 mg/kg de peso corporal.

Formulaciones orales son tabletas o cápsulas particularmente preferidas que pueden formularse por métodos conocidos por las personas expertas en el arte para proporcionar dosis del compuesto activo en el rango de 0.007 mg a 700 mg, por ejemplo 1 mg, 3 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg y 250 mg.

Por lo tanto, de acuerdo con un aspecto adicional de la invención se provee una formulación farmacéutica que incluye cualquiera de los compuestos de la invención, o sus derivados farmacéuticamente aceptables, en mezcla con coadyuvantes, diluyentes y/o excipientes farmacéuticamente aceptables.

Propiedades farmacológicas

Los compuestos de fórmula I son útiles para la normalización de la homeostasis de colesterol, disminuir la absorción del colesterol intestinal, mejorar el transporte reverso de colesterol, mejorar la funcionalidad HDL, incrementar los niveles de colesterol HDL, reducir los niveles de colesterol LDL, disminuir el contenido de colesterol de lipoproteínas con contenido de apoB, estimular la descarga de colesterol de las células vasculares y/o disminuir la respuesta inflamatoria de las células vasculares. Como consecuencia de estas propiedades, se espera que los compuestos de fórmula I tengan efectos anti-arterioscleróticos.

Los compuestos de fórmula I son útiles en la prevención o tratamiento de enfermedad cardiovascular en un mamífero, particularmente un humano. Los compuestos de fórmula I son útiles en la prevención o tratamiento de arteriosclerosis en un mamífero, particularmente un humano. La enfermedad cardiovascular incluye, pero no se limita a, afecciones asociadas con arteriosclerosis, arteriosclerosis, hipercolesterolemia, y otras clases de dislipidemia que aumentan el riesgo de enfermedad cardiovascular. En particular, los compuestos de fórmula I son útiles en el tratamiento o prevención de enfermedad cardiovascular, especialmente las que implican arteriosclerosis, hipercolesterolemia y dislipidemia.

Los compuestos de fórmula I sirven además para prevenir la acumulación de lípidos en, o eliminar lípidos de, depósitos tisulares tales como placas arterioscleróticas o xantomas en un paciente con enfermedad arteriosclerótica, manifestadas por signos clínicos tales como angina, cojera, soplos, que haya sufrido de infarto del miocardio o accidente isquémico transitorio, o cuyo diagnóstico se haya realizado por angiografía, monografía o MRI (Exploración de Resonancia Magnética).

Los compuestos de fórmula I sirven asimismo para prevenir o reducir el riesgo de desarrollar arteriosclerosis, así como para detener o retrasar la evolución de enfermedad arteriosclerótica una vez que se ha hecho clínicamente evidente, lo cual comprende la administración de una cantidad profiláctica o terapéuticamente efectiva, según sea apropiado, de un compuesto de fórmula I a un mamífero, incluido un humano, que se encuentra en riesgo de desarrollar arteriosclerosis o que ya tiene la enfermedad arteriosclerótica.

La arteriosclerosis abarca enfermedades vasculares y afecciones que se reconocen y entienden por los facultativos con práctica en los campos relevantes de la medicina. La enfermedad cardiovascular arteriosclerótica

incluida la restenosis a raíz de intervenciones de revascularización, cardiopatía coronaria (también conocida como arteriopatía coronaria o cardiopatía isquémica), enfermedad cerebrovascular incluida demencia por infartos múltiples, y insuficiencia venosa periférica (***"peripheral vessel disease"***) incluida la disfunción eréctil son todas manifestaciones clínicas de arteriosclerosis y, por consiguiente, están abarcadas por los términos "arteriosclerosis" y "enfermedad arteriosclerótica".

Los presentes compuestos de fórmula (I) son también útiles para la profilaxis y/o tratamiento de afecciones clínicas asociadas con arteriosclerosis tales como hipercolesterolemia inherente o inducida, así como sensibilidad reducida inherente o inducida a la insulina (síndrome de resistencia a la insulina también conocidos como síndrome metabólico) y trastornos metabólicos asociados. Estos trastornos clínicos incluirán, pero no se limitarán a, obesidad general, obesidad abdominal, hipertensión arterial, hiperinsulinemia, hiperglucemia, diabetes tipo 2, diabetes tipo 1 y otras formas raras de diabetes sacarina y la dislipidemia que característicamente se manifiesta con la resistencia a la insulina. Esta dislipidemia, también conocida como el perfil de lipoproteína aterogénica, se caracteriza por ácidos grasos no esterificados moderadamente elevados, partículas ricas en triglicéridos de VLDL elevadas, niveles altos de apolipoproteína B, niveles de bajos de HDL asociados con niveles bajos de apoAI en la presencia de partículas densas y pequeñas de LDL, fenotipo B.

Se espera que los compuestos de la fórmula I sean útiles en tratar pacientes con hiperlipidemias combinadas o mixtas y dislipidemias, especialmente niveles bajos de HDL, con o sin otras manifestaciones del síndrome metabólico.

Se espera que los compuestos de fórmula I sean útiles en tratar pacientes con bajos niveles de HDL de razones distintas al síndrome metabólico o diabetes tipo 2.

Se espera que el tratamiento con los compuestos de fórmula I reduzca la morbimortalidad cardiovascular asociada con arteriosclerosis, debido a sus propiedades antidislipidémicas, así como antinflamatorias. Las cardiopatías vasculares incluyen macro-angiopatías de varios órganos internos que causan infarto del miocardio, insuficiencia cardiaca congestiva, enfermedad cerebrovascular e insuficiencia arterial periférica. Se espera también que el efecto sensibilizante a la insulina de los compuestos de fórmula I prevenga o retrase la evolución de diabetes tipo 2 del síndrome metabólico y diabetes del embarazo. Por lo tanto, se espera que se retrase la evolución de complicaciones de largo plazo asociadas con hiperglucemia crónica en diabetes sacarina, tales como las micro-angiopatías que causan nefropatía, lesión de la retina y vasculopatía periférica de las extremidades inferiores.

Los compuestos de fórmula I pueden ser igualmente útiles para la prevención o tratamiento de inflamación y enfermedades neurodegenerativas o trastornos neuronales. Por consiguiente, esta invención proporciona también un método para prevenir o tratar inflamación en el CNS y un método para prevenir o tratar enfermedades neurodegenerativas o trastornos caracterizados por degeneración neuronal, lesión neuronal o plasticidad deteriorada o inflamación en el CNS. Las enfermedades neurodegenerativas o afecciones caracterizadas por degeneración neuronal e inflamación incluirán, pero no se limitarán a, apoplejía, enfermedad de Alzheimer, demencias fronto-temporales (taupatías), neuropatía periférica, enfermedad de Parkinson, demencia con cuerpos de Lewy, enfermedad de Huntington, esclerosis lateral amiotrófica y esclerosis múltiple.

Los compuestos de fórmula I son útiles en prevenir o tratar dolencias inflamatorias o enfermedades. Estas enfermedades o afecciones incluirán, pero no se limitarán a, enfermedades arterioscleróticas tales como angina pectoris e infarto del miocardio, pero también artritis reumatoide, artritis reumatoide juvenil, lupus sistémico eritematoso, osteoartritis, enfermedad

degenerativa de las articulaciones, una o más enfermedades de tejido conectivo, espondilitis anquilosante, bursitis, síndrome de Sjögren, psoriasis, artritis psórica, neuralgia, sinovitis, glomerulonefritis, vasculitis o sarcoidosis, así como enfermedades inflamatorias del intestino o afecciones tales como enfermedad celíaca, rectitis, gastroenteritis eosinófila, mastocitosis, enfermedad de Crohn, colitis ulcerosa, colitis microscópica, colitis indeterminante, trastorno de intestino irritable, síndrome de intestino irritable y rectitis distal (***"distal proctitis"***). Compuestos de fórmula I pueden usarse asimismo en otras afecciones inflamatorias del pulmón, incluido asma, síndrome disneico agudo del adulto, enfermedad pulmonar obstructiva crónica y ***pneumonia bronchitis***.

Más aún los compuestos de fórmula I pueden ser útiles en el tratamiento de diferentes afecciones fuera del sistema cardiovascular, asociadas o no con resistencia a la insulina, como poliquistosis ovárica, obesidad y cáncer.

La presente invención provee un método de tratar y/o prevenir artritis reumatoide, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir artritis reumatoide juvenil, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir lupus eritematoso sistémico, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir osteoartritis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedad degenerativa de las articulaciones, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir una o más enfermedades de tejido conectivo, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir espondilitis anquilosante, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir bursitis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir síndrome de Sjögren, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir psoriasis, que comprende la administración de una cantidad efectiva de compuesto de

la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir artritis *psórica*, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir neuralgia, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir sinovitis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir glomerulonefritis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir vasculitis o sarcoidosis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedad celíaca, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir rectitis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir gastroenteritis eosinófila, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir mastocitosis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir colitis microscópica, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir colitis indeterminante, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir trastorno de intestino irritable, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedad del intestino inflamado, que comprende la administración de una cantidad

efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir la enfermedad de Crohn, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir colitis ulcerosa, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir síndrome del intestino irritable, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir el síndrome de resistencia a la insulina y/o trastornos metabólicos (como ya se definió), que comprende la administración de un compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir diabetes tipo 2, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedad cardiovascular, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir aterosclerosis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir hipercolesterolemia, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir afecciones asociadas con una necesidad de intensificar el transporte reverso de colesterol, que comprende la administración de una cantidad efectiva de un compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedades asociadas con la necesidad de disminuir la obsorción de colesterol por el intestino, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedades asociadas con una necesidad de aumentar los niveles de colesterol HDL, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedades asociadas con la necesidad de disminuir los niveles de colesterol LDL, que comprende la administración de una cantidad efectiva

de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedades inflamatorias, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedad de Alzheimer, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir arteriosclerosis, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedades asociadas con la necesidad de mejorar la función HDL, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir afecciones hiperlipidémicas, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir enfermedades dislipidémicas, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

La presente invención provee un método de tratar y/o prevenir dislipidemia, que comprende la administración de una cantidad efectiva de compuesto de la fórmula (I) a un mamífero (particularmente un humano) necesitado de ello.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) como un medicamento.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de artritis reumatoide.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de artritis reumatoide juvenil.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de lupus sistémico eritematoso.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de osteoartritis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad degenerativa de las articulaciones.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de una o más enfermedades del tejido conectivo.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de espondilitis anquilosante.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de bursitis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de síndrome de Sjögren.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de psoriasis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de artritis psórica.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de neuralgia.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de sinovitis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de glomerulonefritis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de vasculitis o sarcoidosis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad celíaca.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de rectitis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de gastroenteritis eosinófila.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de mastocitosis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de colitis microscópica.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de colitis indeterminante.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de trastorno del intestino irritable.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad del intestino inflamado.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad de Crohn.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de colitis ulcerosa.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de síndrome del intestino irritable.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedades dislipidémicas.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de resistencia a la insulina y/o trastornos metabólicos.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad cardiovascular.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de aterosclerosis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de hipercolesterolemia.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de intensificar el transporte reverso de colesterol.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de disminuir la absorción de colesterol por el intestino.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de aumentar los niveles de colesterol HDL.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de disminuir los niveles de colesterol LDL.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedades inflamatorias.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad de Alzheimer.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de arteriosclerosis.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de diabetes tipo 2.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de mejorar la función HDL.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones hiperlipidémicas.

En un aspecto adicional, la presente invención provee el uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento y/o profilaxis de dislipidemia.

Terapia de Combinación

Los compuestos de la invención pueden combinarse con otro agente terapéutico que sea útil en el tratamiento de trastornos asociados con el desarrollo y evolución de arteriosclerosis, tales como hipertensión, hiperlipidemias, dislipidemias, diabetes, inflamación y obesidad. Los compuestos de la invención pueden combinarse con otro agente terapéutico

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que disminuya la proporción de LDL:HDL o ApoB:ApoA-1, o un agente que produzca una disminución en los niveles de circulación de colesterol LDL o ApoB o triglicéridos. En pacientes con diabetes sacarina los compuestos de la invención pueden combinarse igualmente con agentes terapéuticos usados para corregir el metabolismo de carbohidratos y tratar complicaciones relacionadas con micro-angiopatías.

En otro aspecto de la presente invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, o su solvato, o un solvato de tal sal, puede administrarse en asociación con inhibidores de la biosíntesis del colesterol, o sus sales farmacéuticamente aceptables, solvatos, o solvatos de tales sales o profármacos. Inhibidores apropiados de la biosíntesis del colesterol incluyen inhibidores de HMG CoA reductasa, inhibidores de la síntesis del escualeno e inhibidores de escualeno epoxidasa. Un inhibidor adecuado de la síntesis del escualeno es escualestatina 1, TAK-475, compuestos descritos en WO2005012284 y un inhibidor de escualeno epoxidasa es NB-598.

En este aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, o su solvato, o un solvato de tal sal, puede administrarse en asociación con un inhibidor de HMG CoA reductasa, o sus sales farmacéuticamente aceptables, solvatos, o solvatos de tales sales o profármacos. Convenientemente un inhibidor de HMG CoA reductasa, o sus sales farmacéuticamente aceptables, solvatos, o solvatos de tales sales o profármacos son estatinas bien conocidas en el arte. Estatinas particulares se seleccionan del grupo conformado por atorvastatina, fluvastatina, pitavastatina, lovastatina, mevastatina, nicostatina, nivastatina, pravastatina y simvastatina, o una sal farmacéuticamente aceptable, en especial de sodio o calcio, solvato, solvato de tal sal o su profármaco. Una estatina particular es atorvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco. Una estatina más particular es sal de calcio de atorvastatina. No obstante, una estatina particularmente preferida es rosuvastatina, o su sal farmacéuticamente aceptable, solvato, solvato de tal

sal o profármaco. Una estatina particular preferible es sal de calcio de rosuvastatina.

En la presente solicitud, el término "inhibidores de la biosíntesis del colesterol" incluye igualmente modificaciones químicas de los inhibidores de HMG-CoA reductasa, inhibidores de la síntesis del escualeno e inhibidores de escualeno epoxidasa, tales como ésteres, profármacos y metabolitos, activos o inactivos.

En otro aspecto de la presente invención, el compuesto de fórmula (I), su sal farmacéuticamente aceptable o su solvato, o un solvato de tal sal, puede administrarse en asociación con un inhibidor del transporte del ácido biliar en el íleon (inhibidor de IBAT), o sus sales farmacéuticamente aceptables, solvatos, o solvatos de tales sales o profármacos.

Se han descrito compuestos apropiados que poseen actividad inhibidora de IBAT; véase por ejemplo los compuestos descritos en WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595 y EP 624 596 y los contenidos de estas solicitudes de patente, se incorporan aquí por referencia.

Además, se han descrito compuestos apropiados que poseen actividad inhibidora de IBAT en WO 94/24087, WO 98/56757, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 02/08211, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, WO 03/091232, WO 03/106482, JP 10072371,

US 5070103, EP 251 315, EP 417 725, EP 869 121, EP 1 070 703 y EP 597 107 y los contenidos de estas solicitudes de patente se incorporan aquí por referencia.

Clases particulares de inhibidores de IBAT apropiados para uso en la presente invención son benzotiepinas, y los compuestos descritos en las reivindicaciones, particularmente la reivindicación 1, de WO 00/01687, WO 96/08484 y WO 97/33882 se incorporan aquí por referencia. Otras clases adecuadas de inhibidores de IBAT son las 1,2-benzotiazepinas, 1,4-benzotiazepinas y 1,5-benzotiazepinas. Una clase adicional apropiada de inhibidores de IBAT son las 1,2,5-benzotiadiazepinas.

Un compuesto particular apropiado que posee actividad inhibidora IBAT es ácido (3*R*,5*R*)-3-butil-3-etil-1,1-dióxido-5-fenil-2,3,4,5-tetrahidro-1,4-benzotiazepin-8-il β-D-glucopiranosidurónico (EP 864 582). Un compuesto apropiado adicional que posee actividad inhibidora IBAT es S-8921 (EP 597 107).

En otro aspecto de la presente invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, o su solvato, o un solvato de tal sal, puede administrarse en asociación con un antagonista de absorción de colesterol, o sus sales farmacéuticamente aceptables, solvatos, o solvatos de tales sales o profármacos, por ejemplo AVE-5530 o por ejemplo azetidinonas tales como ezetrol (zetia, ezetimibe) y los descritos en US 5,767,115, que se incorporan aquí por referencia. Se han descrito compuestos apropiados que poseen actividad antagonista de absorción de colesterol; véase, por ejemplo los compuestos descritos en WO 02/50027, WO 02/66464, WO 04/005247, WO 04/000803, WO 04/000804 y WO 04/000805, WO05021495, WO05021497 y WO05033100 las cuales se incorporan aquí por referencia.

En otro aspecto de la presente invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, o su solvato, o un solvato de tal sal, puede

administrarse en asociación captador de ácido biliar (***"a bile acid sequestrant"***) o sus sales farmacéuticamente aceptables, solvatos, o solvatos de tales sales o profármacos. Captadores apropiados de ácido biliar incluyen HBS-107, colestiramina (Questran®, LoCholest®), colestemida (Cholebine®), colesevelam (Welchol®), colestipol (Colestid®) y cosevelam clorhidrato.

En otro aspecto de la presente invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con otros agentes que aumentan el transporte reverso de colesterol por medios distintos a incrementar la expresión de transportadores de ABC, por ejemplo miméticos de ApoA-1. Véase por ejemplo los compuestos descritos en WO-2004094471, que se incorporan en esta solicitud por referencia. Miméticos apropiados de ApoA-1 incluyen D-F4, ETC 216, ETC 642, RTC 588, ETC 1001, Apo Al Milano, D-4F y AVP-26452.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un agente modulador del receptor activado por el factor proliferante de peroxisomas (PPAR). Los agentes moduladores de PPAR incluyen un agonista de PPAR alfa y/o gamma y/o delta, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos. Agonistas apropiados de PPAR alfa y/o gamma, y/o delta, sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos son bien conocidos en el arte. Éstos incluyen los compuestos descritos en WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, WO 04/000790, WO 04/000295, WO 04/000294, WO 03/051822, WO 03/051821, WO 02/096863, WO 03/051826, WO 02/085844, WO 01/40172, J Med Chem, 1996, 39, 665, Concepto Experto sobre Patentes Terapéuticas, 10 (5), 623-634 (en particular los compuestos descritos en las solicitudes de patente

listadas en la página 634) y J Med Chem, 2000, 43, 527, las cuales se incorporan todas aquí por referencia. Particularmente un agonista PPAR alfa y/o gamma y/o delta se refiere a muraglitazar (BMS 298585), rivoglitazona (CS-011), netoglitazona (MCC-555), balaglitazona (DRF-2593, NN-2344), clofibrato (Atromid-S®), fenofibrato, bezafibrato (Oralipin®), gemfibrozil (Lopid®), ciprofibrato (Ciprol®), pioglitazona (Actos®), rosiglitazona (Avandia®), AVE-0847, AVE-8134, CLX-0921, DRF-10945, DRF-4832, E-3030, K-111, KRP-101, LBM-642 (oxeglitazar), LY-518674, LY-674, naveglitazar (LY-818), LY-929, 641597, GW-590735, GW-677954, GW-501516, metaglidasan (MBX-102), MBX-2044, ONO-5129, PLX-204, R-483 (BM131258), R-119702, T-131 (AMG-131), TAK-559 ó TAK-654. Particularmente un agonista de PPAR alfa y/o gamma y/o delta se refiere a tesaglitazar ácido (S)-2-etoxi-3-[4-(2-{4-metanosulfoniloxifenil}etoxi)-fenil]propanoico y sus sales farmacéuticamente aceptables.

En todavía otro aspecto de la invención, el compuesto de fórmula (I), o su sal farmacéuticamente aceptable, o su solvato, o un solvato de tal sal, puede administrarse en asociación con un inhibidor de piruvato dehidrogenasa cinasa (PDK), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un inhibidor de proteína de transporte de colesteril éster (CETP, ***cholesteryl ester transfer protein***), o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, por ejemplo los referenciados y descritos en WO 00/38725 página 7 renglón 22 – página 10, renglón 17, que se incorporan aquí por referencia.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un inhibidor de proteína de transporte de triglicéridos microsómicos (MTP, ***microsomal-triglyceride transfer protein***), o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, por ejemplo implipatide y los descritos en WO 03/004020, WO 03/002533, WO 02/083658 y WO 00/242291, y los contenidos de estas solicitudes de patente se incorporan aquí por referencia, o los descritos en Science, 282, 751-54, 1998, que se incorporan aquí por referencia.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un agonista al receptor HM74A (receptor de ácido nicotínico). Ejemplos de agonistas HM74A son, por ejemplo, los compuestos descritos en WO2005011677, WO2004032928, WO2004033431 o un derivado de ácido nicotínico, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, incluidos productos de combinación y liberación lenta, por ejemplo, ácido nicotínico (niacina), acipimox, nicofuranosa, NIASPAN® y niceritrol.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un inhibidor de acil coenzima A: colesterol O-aciltransferasa (ACAT, ***acyl coenzymA: cholesterol O-acyltransferase***), o ACAT2 o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, por ejemplo CS-505, eflucimibe (F-12511), K-604 y SMP-797.

En aún otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede

administrarse en asociación con moduladores de receptores hormonales nucleares tales como receptor farnesoide X (FXR), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco, por ejemplo EMT-747, o moduladores de receptores nucleares tales como el receptor X retenoide (RXR), o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o profármaco.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un compuesto de fitosterol, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, por ejemplo estanoles y FM- VP4.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con otras terapias para el tratamiento del síndrome metabólico o diabetes tipo 2 y sus complicaciones asociadas, éstos incluyen fármacos de biguanida, por ejemplo metformina, fenformina y buformina, insulina (análogos de insulina sintética, amilina) y antihiperglucémicos orales (éstos se dividen en reguladores de glucosa prandial e inhibidores de alfa-glucosidasa). Un ejemplo de un inhibidor de alfa-glucosidasa es acarbosa o voglibosa o miglitol. Un ejemplo de un regulador de glucosa prandial es repaglinida o nateglinida.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con una sulfonilurea por ejemplo: glimepirida, glibenclamida (gliburida), gliclazida, glipizida, gliquidona, cloropropamida, tolbutamida, acetohexamida, glicopiramida, carbutamida, glibonurida, glisoxepid, glibutiazol, glibuzol, glihexamida, glimidina, glipinamida, fenbutamida, tolcilamida y tolazamida. Preferiblemente, la sulfonilurea es glimepirida o glibenclamida (gliburida). Más preferiblemente, la

sulfonilurea es glimepirida. Por lo tanto, la presente invención incluye la administración de un compuesto de la presente invención en conjunción con una, dos o más terapias existentes descritas en este párrafo. Las dosis de las demás terapias existentes para el tratamiento de diabetes tipo 2 y sus complicaciones asociadas serán aquellas conocidas en el arte y aprobadas para uso por los organismos de control, por ejemplo la FDA y pueden encontrarse en el Orange Book publicado por la FDA. Alternativamente, pueden usarse dosis más pequeñas como resultado de los beneficios derivados de la combinación.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un compuesto antihipertensor, por ejemplo altiazida, benztiazida, captopril, carvedilol, clorotiazida sódica, clorhidrato de clonidina, ciclotiazida, clorhidrato de delapril, clorhidrato de dilevalol, mesilato de doxazosina, fosinopril sódico, clorhidrato de guanfacina, metiidopa, metoprolol succinato, clorhidrato de moexipril, monatepil maleato, clorhidrato de pelanserina, clorhidrato de fenoxibenzemina, clorhidrato de prazosina, primidolol, clorhidrato de quinapril, quinaprilat, ramipril, clorhidrato de terazosina, candesartán, candesartán cilexetil, telmisartan, amlodipina besilato, amlodipina maleato y clorhidrato de bevantolol, o sus sales farmacéuticamente aceptables, o solvatos, o solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un inhibidor de enzima convertidora de angiotensina (ACE). Inhibidores particulares de ACE o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, incluidos metabolitos activos, que pueden usarse en combinación con un compuesto de la fórmula (I), incluyen, pero no se limitan a, los siguientes compuestos: alacepril, alatriopril, ancovenina,

benazepril, clorhidrato de benazepril, benazeprilat, benzoilcaptopril, captopril, captopril-cisteína, captopril-glutatión, ceranopril, cilazapril, cilazaprilat, delapril, delapril-diácido, enalapril, enalaprilat, enapril, epicaptopril, foroximitina, fosfenopril, fosenopril, fosenopril sódico, fosinopril, fosinopril sódico, fosinoprilat, ácido fosinoprílico, hemorfin-4, imidapril, indolapril, indolaprilat, lisinopril, liciumina A, liciumina B, moexipril, moexiprilat, muraceína A, muraceína B, muraceína C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, clorhidrato de quinapril, quinaprilat, ramipril, ramiprilat, spirapril, clorhidrato de espirapril, espiraprilat, espiropril, clorhidrato de espiropril, temocapril, clorhidrato de temocapril, teprotide, trandolapril, trandolaprilat, zofenopril y zofenoprilat. Inhibidores preferidos de ACE para uso en la presente invención son ramipril, ramiprilat, lisinopril, enalapril y enalaprilat. Inhibidores de ACE más preferidos para usos en la presente invención son ramipril y ramiprilat.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con un antagonista de receptor de angiotensina II. Antagonistas preferidos de receptor de angiotensina II, sus sales farmacéuticamente aceptables, solvatos, solvato de tales sales o profármacos para uso en combinación con un compuesto de la fórmula (I) incluyen, pero no se limitan a, los compuestos: candesartán, candesartán cilexetil, losartán, valsartán, irbesartán, telmisartán y eprosartán. Antagonistas particularmente preferidos de receptor de angiotensina II o sus derivados farmacéuticamente aceptables para uso en la presente invención son candesartán y candesartán cilexetil o sus sales farmacéuticamente aceptables, solvatos, solvato de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede

administrarse con un bloqueador. Bloqueadores andrenérgicos incluyen un bloqueador α-adrenérgico, o un bloqueador β-adrenérgico, o un bloqueador α/β-adrenérgico mixto o sus sales farmacéuticamente aceptables, solvatos, solvato de tales sales o profármacos. Ejemplos de bloqueadores adrenérgicos son tosilato de bretilio, dihidroergotamina mesilato, fentolamina mesilato, solipertina tartrato, clorhidrato de zolertina, carvedilol, clorhidrato de labetalol, clorhidrato de fenspirida, clorhidrato de labetalol, proroxan, clorhidrato de alfuzosina, acebutolol, a clorhidrato de cebutolol, clorhidrato de alprenolol, atenolol, clorhidrato de bunolol, clorhidrato de carteolol, clorhidrato de celiprolol, clorhidrato de cetamolol, clorhidrato de cicloprolol, clorhidrato de dexpropranolol, clorhidrato de diacetolol, clorhidrato de dilevalol, clorhidrato de esmolol, clorhidrato de exaprolol, sulfato de flestolol, clorhidrato de labetalol, clorhidrato de levobetaxolol, clorhidrato de levobunolol, clorhidrato de metalol, metoprolol, tartrato de metoprolol, nadolol, sulfato de pamatolol, sulfato de penbutolol, practolol, clorhidrato de propranolol, clorhidrato de sotalol, timolol, maleato de timolol, clorhidrato de tiprenolol, tolamolol, bisoprolol, fumarato de bisoprolol y nebivolol o sus sales farmacéuticamente aceptables, solvatos, solvato de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con un estimulante adrenérgico, por ejemplo, un producto de combinación de clorotiazida y metildopa, el producto de combinación de metiidopa hidroclorotiazida y metildopa, clorhidrato de clonidina, clonidina, el producto de combinación de clorotalidona y clorhidrato de clonidina y clorhidrato de guanfacina, o sus sales farmacéuticamente aceptables, solvatos, solvato de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede

administrarse en asociación con un bloqueador de canal de calcio, por ejemplo clentiazem maleato, besilato de amlodipina, isradipina, nimodipina, felodipina, nilvadipina, nifedipina, clorhidrato de teludipina, clorhidrato de diltiazem, belfosdil, clorhidrato de verapamil o fostedil, o un bloqueador AT-1, o un salurético, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con un diurético, por ejemplo, el producto de combinación de hidroclorotiazida y espironolactona y el producto de combinación de hidroclorotiazida y triamterene, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con unvasodilator, por ejemplo, vasodilatadores coronarios (por ejemplo fostedil, clorhidrato de azaclorzina, clorhidrato de cromonar, clonitrato, clorhidrato de diltiazem, dipiridamol, droprenilamina, eritritil tetranitrato, dinitrato de isosorbida, mononitrato de isosorbida, lidoflazina, clorhidrato de mioflazina, mixidina, molsidomina, nicorandil, nifedipina, nisoldipina, nitroglicerina, clorhidrato de oxprenolol, pentrinitrol, maletao de perhexilina, prenilamina, nitrato de propatil, clorhidrato de terodilina, tolamolol y verapamil), o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con agentes anti-anginales, por ejemplo, besilato de amlodipina, maleato de amlodipina, clorhidrato de betaxolol, clorhidrato de bevantolol, clorhidrato de butoprozina, carvedilol, maleato de

cinepazet, succinato de metoprolol, molsidomina, maleato de monatepil, primidolol, clorhidrato de ranolazina, tosifen o clorhidrato de verapamil o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal puede administrarse en asociación con anti-coagulantes seleccionados de argatroban, bivalirudina, dalteparina sódica, desirudina, dicumarol, Iyapolato sódico, mesilato de nafamostat, phenprocoumon, tinzaparina sódica y warfarina sódica o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal puede administrarse en asociación con agentes anti-trombóticos, por ejemplo clorhidrato de anagrelida, bivalirudina, cilostazol, dalteparina sódica, danaparoid sódico, clorhidrato de dazoxiben, sulfato de efegatran, enoxaparina sódica, fluretofen, ifetroban, ifetroban sódico, lamifiban, clorhidrato de lotrafiban, napsagatran, acetato de orbofiban, acetato de roxifiban, sibrafiban, tinzaparina sódica, trifenagrel, abciximab y zolimomab aritox o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal puede administrarse en asociación con otros agentes que actúan como o suministran un agonista de factor IIa, por ejemplo 3DP-4815, AZD-0837, melagatran, ximelagatran, ART-123, lepirudina, AVE-5026, bivaluridina, dabigatran etexilato, E-4444, odiparcil, ardeparina sódica, pegmusirudina, LB-30870, sulfato de dermatan, argatroban, MCC-977, desirudina, deligoparina sódica, PGX-100, idraparinux sódico, SR-123781, SSR-

182289A, SCH-530348, TRIB50, TGN-167, TGN-255, y los compuestos descritos en WO94/29336, WO97/23499 y WO02/44145, los cuales se incorporan en esta solicitud por referencia.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con antagonistas de receptor de fibrinógeno, por ejemplo acetato de roxifiban, fradafiban, orbofiban, clorhidrato de lotrafiban, tirofiban, xemilofiban, anticuerpo monoclonal 7E3 y sibrafiban o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con un inhibidores plaquetarios, por ejemplo cilostezol, bisulfato de clopidogrel, epoprostenol, epoprostenol sódico, clorhidrato de ticlopidina, aspirina, ibuprofeno, naproxeno, sulindae, indometacina, mefenamato, droxicam, diclofenac, sulfinpirazona y piroxicam, dipiridamol o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con inhibidores de agregación plaquetaria, por ejemplo acadesina, beraprost, beraprost sódico, ciprostene cálcico, itezigrel, lifarizina, clorhidrato de lotrafiban, acetato de orbofiban, oxagrelate, fradafiban, orbofiban, tirofiban y xemilofiban o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede

administrarse en asociación con agentes hemorreológicos, por ejemplo pentoxifilina o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal puede administrarse en asociación con inhibidores de coagulación asociada con lipoproteína; o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con un inhibidor de Factor VIIa o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con un inhibidor de Factor Xa o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, puede administrarse en asociación con una heparina de bajo peso molecular, por ejemplo enoxaparina, nardroparina, dalteparina, certroparina, parnaparina, reviparina y tinzaparina o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos.

En otro aspecto de la invención, el compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal puede administrarse en asociación con un compuesto anti-obesidad, o sus sales

farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, por ejemplo un inhibidor de lipasa pancreática, por ejemplo orlistat (EP 129,748), ATL-962, GT-389255 o una sustancia para controlar el apetito (saciedad), por ejemplo sibutramina (Meridia® , Reductil® , GB 2,184,122 y US 4,929,629), PYY 3-36 (amilina), APD-356, 1426, Axokine, T-71, un antagonista de cannabinoide 1 (CB1) o agonista inverso, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, por ejemplo rimonabant (EP 656354), AVE-1625, CP945598, SR-147778, SLV-319, y como se describe en WO 01/70700, o un inhibidor de Síntesis de Ácidos Grasos (FAS), o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos o un antagonista de la hormona concentradora de melanina (MCH), o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, por ejemplo 856464 y como se describe en WO 04/004726.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un agente antiinflamatorio tales como glucocorticoides, agentes antinflamatorios no esteroides (AINE) o agentes antinflamatorios intestinales, o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos. Glucocorticoides apropiados incluirán, pero no se limitarán a, betametasona, dexametasona, metilprednisolona, prednisolona, prednisona, triamcinolona, hidrocortisona, cortisona y budesonida. Agentes anti-inflamatorios no esteroides adecuados incluirán, pero no se limitarán a indometacina, diclofenac, ibuprofeno así como ácido acetilsalicílico. Agentes antinflamatorios intestinales apropiados incluirán, pero no se limitarán a, aminosalicilatos tales como sulfasalazina, mesalazina, olsalazina y balsalazida.

En otro aspecto de la invención, el compuesto de la fórmula (I), o su sal farmacéuticamente aceptable, o solvato, o solvato de tal sal, puede administrarse en asociación con un inhibidor de colinesterasa o un

antagonista de receptor de N-metil-D-aspartato (NMDA), o sus sales farmacéuticamente aceptables, solvatos, solvatos de tales sales o profármacos, tales como donepezil, rivastigmina o galantamina o memantina.

Por lo tanto, en una característica adicional de la invención, se provee un método de tratar y/o prevenir trastornos metabólicos en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o un solvato de tal sal, en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

Por lo tanto, en una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de diabetes tipo 2 y sus complicaciones asociadas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal, en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

Por lo tanto en una característica adicional de la invención, se provee un método de tratar y/o prevenir enfermedades hiperlipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o

separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de dislipidemia en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal, en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis del síndrome de resistencia a la insulina en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula I, o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal, en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de enfermedad cardiovascular en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos

descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de aterosclerosis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de hipercolesterolemia en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para tratar y/o prevenir afecciones asociadas con una necesidad de mejorar el transporte reverso de colesterol en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de

combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para tratar y/o prevenir dolencias asociadas con una necesidad de disminuir la absorción de colesterol en el intestino en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para tratar y/ prevenir afecciones asociadas con una necesidad de incrementar los niveles de colesterol HDL en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para tratar y/o prevenir enfermedades asociadas con una necesidad de disminuir niveles de colesterol LDL en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad

efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de dolencias inflamatorias en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de enfermedad de Alzheimer en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de arteriosclerosis un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula I, o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de

combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para tratar y/o prevenir afecciones asociadas con una necesidad de mejorar la función HDL en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de artritis reumatoide en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de artritis reumatoide juvenil en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos

descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de lupus sistémico eritematoso en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de osteoartritis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de enfermedad degenerativa de las articulaciones en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de una o más enfermedades del tejido conectivo en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de espondilitis anquilosante en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de bursitis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de síndrome de Sjögren en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de psoriasis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de artritis *psórica* en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de neuralgia en un animal de sangre caliente, tal

como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de sinovitis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de glomerulonefritis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de vasculitis o sarcoidosis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la

fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de enfermedad celíaca en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de rectitis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de gastroenteritis eosinófil en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad

efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de mastocitosis en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de colitis microscópica en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de colitis indeterminante en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de

combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de trastorno de intestino irritable en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de enfermedad del intestino inflamado en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de enfermedad de Crohn en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de colitis ulcerosa en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de síndrome de intestino irritable en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

En una característica adicional de la invención, se provee un método para el tratamiento y/o profilaxis de enfermedades dislipidémicas en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal en administración simultánea, consecutiva o separada con una cantidad efectiva de uno de los demás compuestos descritos en esta sección de combinación, o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco.

De acuerdo con un aspecto adicional de la invención se provee una composición farmacéutica, que comprende un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco, en asociación con un diluyente o excipiente farmacéuticamente aceptable.

De acuerdo con un aspecto adicional de la presente invención se provee un kit que comprende un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco.

De acuerdo con un aspecto adicional de la presente invención se provee un kit que comprende:

a) un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal, en una primera presentación farmacéutica unitaria;

b) uno de los demás compuestos descritos en esta sección de combinación o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su profármaco, en una segunda presentación farmacéutica unitaria; y

c) medios de envase para contener dichas presentaciones farmacéuticas unitarias primera y segunda.

De acuerdo con un aspecto adicional de la presente invención se provee un kit que comprende:

a) un compuesto de la fórmula I, o su sal farmacéuticamente aceptable o solvato, o solvato de tal sal, junto con un diluyente o excipiente farmacéuticamente aceptable, en una primera presentación farmacéutica unitaria;

b) uno de los demás compuestos descritos en esta sección de combinación o su sal farmacéuticamente aceptable, solvato, solvato de tal sal o su

profármaco, en una segunda presentación farmacéutica unitaria; y
c) medios de envase para contener dichas presentaciones farmacéuticas unitarias primera y segunda.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de trastornos metabólicos y sus complicaciones asociadas en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de síndrome metabólico o diabetes tipo 2 y sus complicaciones asociadas en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de dislipidemia en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o

un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedades hiperlipidémicas en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedad cardiovascular en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de aterosclerosis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de hipercolesterolemia en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o

un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de intensificar el transporte reverso de colesterol en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de disminuir la absorción del colesterol en el intestino en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de incrementar los niveles de colesterol HDL en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de afecciones asociadas con una

necesidad de reducir los niveles de colesterol LDL en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedades inflamatorias en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedad de Alzheimer en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de arteriosclerosis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento

para uso en el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de mejorar la función HDL en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de artritis reumatoide en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de artritis reumatoide juvenil en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de lupus sistémico eritematoso en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable,

solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de osteoartritis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis enfermedad degenerativa de las articulaciones en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de una o más enfermedades del tejido conectivo en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de espondilitis anquilosante en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable,

solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de bursitis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de síndrome de Sjögren en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de psoriasis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de artritis *psórica* en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable,

solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de neuralgia en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de sinovitis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de glomerulonefritis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de vasculitis o sarcoidosis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable,

solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedad celíaca en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de rectitis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de gastroenteritis eosinófila en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención, se provee el uso de un compuesto de la fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de mastocitosis en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable,

solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de colitis microscópica en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de colitis indeterminante en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de trastorno de intestino irritable en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedad del intestino inflamado en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable,

solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedad de Crohn en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de colitis ulcerosa en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de síndrome de intestino irritable en un animal de sangre caliente, tal como el hombre.

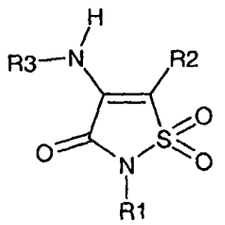
De acuerdo con otra característica de la invención se provee el uso de un compuesto de fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, y uno de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, en la fabricación de un medicamento para uso en el tratamiento y/o profilaxis de enfermedades dislipidémicas en un animal de sangre caliente, tal como el hombre.

De acuerdo con un aspecto adicional de la presente invención se provee un tratamiento de combinación que comprende la administración de una cantidad efectiva de un compuesto de la fórmula (I), o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, opcionalmente junto

con un diluyente o excipiente farmacéuticamente aceptable, con la administración simultánea, consecutiva o separada de una cantidad efectiva de los demás compuestos descritos en esta sección de combinación, o su sal o solvato farmacéuticamente aceptable, solvato de tal sal o su profármaco, opcionalmente junto con un diluyente o excipiente farmacéuticamente aceptable a un animal de sangre caliente tal como el hombre necesitado de tal tratamiento terapéutico.

Otros aspectos de la invención

Aspecto adicional 1. Un compuesto de fórmula general I



o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal, en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$; cicloalquilo o heterociclilo sustituido cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$; fenilo o heteroarilo sustituido cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b,

$S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^2 representa

fenilo, que se sustituye opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituyen cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

E o Het^4 sustituido cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 cada uno se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$; y en las anteriores definiciones

X representa un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono en donde dicho grupo alquilo puede interrumpirse opcionalmente por O, S, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2;

Y se une a nitrógeno en la posición 2 en el 1,1-dióxido de isotiazol-3(2*H*)-ona y representa un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 3 átomos de carbono en donde dicho grupo alquilo puede interrumpirse o terminarse opcionalmente por O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c y/o Y se sustituye opcionalmente por uno o más de los siguientes: OH, F, CN, NR^aR^a, C_1-C_4alquilo, OR^b, SR^b, $S(O)R^b$ o SO_2R^b;

Z se une a E o Het^4 y uno de los siguientes: Q, Het^1, R o Het^2, y representa un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono en donde dicho grupo alquilo puede interrumpirse o terminarse opcionalmente por O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, consta opcionalmente sólo de uno de los siguientes: O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a , SO_2NR^a, NR^aSO_2 y/o Z se sustituye opcionalmente por uno o más de los siguientes: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $S(O)R^c$, SO_2R^c, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b, OR^b;

M representa un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un anillo bicíclico no aromático o parcialmente aromático, saturado o insaturado compuesto de 4, 5, 6, 7, 8, 9 ó 10 átomos de carbono;

E representa un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un anillo bicíclico no aromático o parcialmente aromático, saturado o insaturado compuesto de 4, 5, 6, 7, 8, 9 ó 10 átomos de carbono, y el anillo se une, a menos que se especifique lo contrario, a través de su parte no aromática a nitrógeno en la posición 4 en el 1,1-dióxido de isotiazol-3(2*H*)-ona;

A representa un anillo monocíclico aromático, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un anillo bicíclico aromático compuesto de 4, 5, 6, 7, 8, 9 ó 10 átomos de carbono;

P se une a nitrógeno en la posición 4 en el 1,1-dióxido de isotiazol-3(2*H*)-ona y representa un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono en donde el grupo alquilo se interrumpe o termina opcionalmente por O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 y/o P se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $S(O)R^b$, SO_2R^b, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b o OR^b;

Q representa un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7, 8 átomos de carbono, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R representa un grupo fenilo, que se sustituye opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

T se une a M, Het^3, A o Het^5 y representa un grupo alquilo con 1 átomo de carbono o consiste opcionalmente de uno o más de los siguientes: O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2;

Het^1 representa un anillo monocíclico de 3-10 miembros, no aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, y en donde el anillo se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$,

$C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

Het^2 representa un anillo monocíclico de 3-10 miembros, aromático, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno y azufre, y el cual se sustituye por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

Het^3 representa un anillo monocíclico de 3-10 miembros, no aromático, saturado o insaturado o un anillo bicíclico de 4-10 miembros, no aromático o parcialmente aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo monocíclico o bicíclico es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre;

Het^4 representa un anillo monocíclico de 3-10 miembros, no aromático, saturado o insaturado o un anillo bicíclico de 4-10 miembros, no aromático o parcialmente aromático, saturado o insaturado en el cual uno o más de los átomos en el anillo monocíclico o bicíclico es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, y el anillo se une, a menos que se especifique lo contrario, a través de su parte no aromática a nitrógeno en la posición 4 en el 1,1-dióxido de isotiazol-3(2*H*)-ona;

Het^5 representa un anillo monocíclico de 3-10 miembros, aromático o un anillo bicíclico de 4-10 miembros, aromático en el cual uno o más de los átomos en el anillo monocíclico o bicíclico es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre;

R^a representa independientemente H o una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F;

R^b representa independientemente una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F; y R^c representa independientemente H o una cadena C_1-C_3alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.

Aspecto adicional 2. Un compuesto de acuerdo con aspecto adicional 1 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde
R^1 representa
X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b o $C(O)R^b$;
cicloalquilo o heterociclilo sustituido cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b o $C(O)R^b$;
fenilo o heteroarilo sustituido cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;
cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;
fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 representa
fenilo, que se sustituye opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

Aspecto adicional 3. Un compuesto de acuerdo con aspecto adicional 2 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde
R^1 representa
X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 4. Un compuesto de acuerdo con aspecto adicional 3 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde
R^1 representa
X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b o $C(O)R^b$.

Aspecto adicional 5. Un compuesto de acuerdo con aspecto adicional 1 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde
R^3 representa
X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$,

$OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 6. Un compuesto de acuerdo con aspecto adicional 1 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,

en donde

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o

C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 7. Un compuesto de acuerdo con aspecto adicional 1 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde
R^3 representa
E o Het^4 sustituido cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$,
y E o Het^4 cada uno se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 8. Un compuesto de acuerdo con aspecto adicional 2 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde
R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 9. Un compuesto de acuerdo con aspecto adicional 2 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,

en donde

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$,

$C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 10. Un compuesto de acuerdo con aspecto adicional 2 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde
R^3 representa
E o Het^4 sustituido cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,
y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^2SO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 11. Un compuesto de acuerdo con aspecto adicional 3 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,
en donde

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 12. Un compuesto de acuerdo con aspecto adicional 3 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,

en donde

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b,

SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 13. Un compuesto de acuerdo con aspecto adicional 3 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,

en donde

R^3 representa

E o Het^4 sustituido cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 14. Un compuesto de acuerdo con aspecto adicional 4 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,

en donde

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 15. Un compuesto de acuerdo con aspecto adicional 4 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,

en donde

R^3 representa

MP o Het^3P en donde M y Het^3 cada uno de los cuales se sustituye opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 16. Un compuesto de acuerdo con aspecto adicional 4 o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal,

en donde

R^3 representa

E o Het^4 sustituido cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

Aspecto adicional 17. Un compuesto de acuerdo con aspecto adicional 1 en el cual R^1 se selecciona de etilo, isopropilo, n-butilo, *terc*-butilo, ciclopentilo, hexilo, bencilo, 2-metoxietilo, piridin-2ilmetilo, piridin-3-ilmetilo, piridin-4-ilmetilo, tetrahidrofuran-2-ilmetilo o 2-(3-fluorofenil)etilo;

R^2 es fenilo; y

R^3 se selecciona de butilo, hexilo, bencilo, 3-[3-(hidroximetil)fenoxi] propilo, 4-fenilbutilo, 3-(2-metoxifenoxi)propilo, 3-[4-(hidroximetil) fenoxi]propilo, 3-(2-fluorofenoxi)propilo, 3-(2-clorofenoxi)propilo, 3-(3-metoxifenoxi)propilo, 3-(piridin-3-iloxi)propilo, 3-(piridin-4-iloxi)propilo, 1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 3-(feniltio)propilo, 3-fenoxipropilo, 3-(3-clorofenoxi)propilo, 3-(3- fluorofenoxi)propilo, 3-(4-fluorofenoxi)propilo, 1-[4-(trifluorometil)pirimidin-2-il]piperidin-4-ilo, *cis*-4-hidroxiciclohexilo, 4-fenoxibutilo, 3-[(1-oxidopiridin-3-il)oxi]propilo, 3-(4-metoxifenoxi)propilo, 4,4-difluorociclohexilo, 2-fenoxietilo, 2-feniletilo, 4-(difluorometoxi)bencilo, *trans*-4-hidroxiciclohexilo, 3-hidroxipropilo, 2,3-dihidro-1,4-benzodioxin-2-ilmetilo, 4-hidroxiciclohexilo, 3-(4-clorofenoxi)propilo, 1,3-benzodioxol-5-ilmetilo, 2,3-dihidro-1*H*-inden-2-ilo, 2-(morfolin-4-il)etilo, 3-(4- isopropilfenoxi) propilo, 3-[bencil(butil)amino]propilo, 3-(3,5-dipropoxifenoxi)propilo, 2,2-difeniletilo, 2-(1*H*-imidazol-4-il)etilo, 4-morfolin-4-ilbencilo, 3-(2-metoxietoxi)propilo, 3-morfolin-4-ilpropilo, 2-metoxietilo, tetrahidro-2H-piran-4-ilo, 4-hidroxiciclohexilo, 4-metoxibencilo, 3-(3-hidroxifenoxi)propilo, 3-(3-acetamidofenoxi)propilo, 3-(4-*N*,*N*-dimetilaminocarbonilmetilfenoxi)propilo, 3-(3-carboximetilfenoxi)propilo, 3-(3-metoxicarbonilmetilfenoxi)propilo, 3-(3-metoxicarbonilfenoxi)propilo, 3-(4-carboximetilfenoxi)propilo, 3-(4-metoxicarbonilmetilfenoxi)propilo, 3-(3-acetilaminofenoxi)propilo, 3-(4-hidroxifenilcarboxi)propilo, 3-(4-carboxifenoxi)propilo o 1-(2-nitriloetil)piperidin-4-ilo.

Aspecto adicional 18. Un compuesto seleccionado de uno o más de los siguientes:

1,1-dióxido de 2-*terc*-butil-4-({3-[3-(hidroximetil)fenoxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil]-4-{[3-(2-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({3-[4-(hidroximetil)fenoxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

N-(3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetamida

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

2-(4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)-N,N-dimetilacetamida

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

ácido (3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acético

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-3-iloxi)propil]amino} isotiazol-3(2*H*)-ona

metil (3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-4-iloxi)propil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il}amino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-ciclopentil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(feniltio)propil]amino}isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(3-fenoxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

metil 3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoato

1,1-dióxido de 2-bencil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

ácido (4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acético

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-fluorofenoxi)propil]amino}-5-fenilisotiazol-3-(2*H*)-ona

metil (4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-({1-[4-(trifluorometil)pirimidin-2-il]piperidin-4-il} amino)isotiazol-3(2*H*)-ona

N-(3-{3-[(2-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetamida

3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] propil 4-hidroxibenzoato

1,1-dióxido de 4-(bencilamino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-[2-(3-fluorofenil)etil]-5-fenil-4-[(4-fenilbutil)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(cis-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(4-fenoxibutil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({3-[(1-oxidopiridin-3-il)oxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-ciclopentil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(4,4-difluorociclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(tetrahidrofuran-2-ilmetil) isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-(hexilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-{[4-(difluorometoxi)bencil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(trans-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(3-hidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-3-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,3-dihidro-1,4-benzodioxin-2-ilmetil) amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-hidroxiciclohexil)amino]-5-fenilisotiazol-3(2*H*)-ona

ácido 4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoico

3-{4-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}propanonitrilo

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-4-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-(2,3-dihidro-1*H*-inden-2-ilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(2-morfolin-4-iletil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-isopropilfenoxi)propil]amino}-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 4-({3-[bencil(butil)amino]propil}amino)-2-*terc*-butil-5-fenilisotiazol-3-(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3,5-dipropoxifenoxi)propil]amino}-5-fenilisotiazol-3-(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,2-difeniletil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-etil-4-{[2-(1H-imidazol-4-il)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-morfolin-4-ilbencil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-{[3-(2-metoxietoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(3-morfolin-4-ilpropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(2-metoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-(2-metoxietil)-5-fenil-4-(tetrahidro-2*H*-piran-4-ilamino) isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(hexilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(4-hidroxiciclohexil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-metoxibencil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-2-ilmetil)isotiazol-3(2*H*)-ona

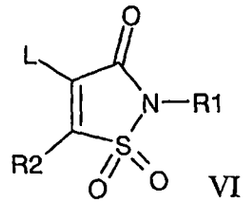
1,1-dióxido de 2-*terc*-butil-4-{[3-(3-hidroxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

ácido 3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}benzoico

o su sal o solvato farmacéuticamente aceptable, o un solvato de tal sal.

Aspecto adicional 19. Un proceso para la preparación de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18, en donde R^1, R^2 o R^3 son como se definen en la reivindicación 1, que comprende el paso de hacer reaccionar

un compuesto de fórmula VI,



VI

en donde R^1 y R^2 son como se definen en la reivindicación 1 y L es un grupo saliente tal como Cl, Br, I, metanosulfonato o trifluorometanosulfonato, con un compuesto de fórmula VII,

$$R^3NH_2 \quad VII$$

en donde R^3 es como se define en la reivindicación 1, opcionalmente en la presencia de un disolvente orgánico inerte tal como dimetilformamida.

Aspecto adicional 20. Una formulación farmacéutica que comprende un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18

en mezcla con coadyuvantes, diluyentes y/o excipientes farmacéuticamente aceptables.

Aspecto adicional 21. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en terapia.

Aspecto adicional 22. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 para la fabricación de un medicamento para la modulación de los receptores hormonales nucleares LXR α y/o β.

Aspecto adicional 23. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad cardiovascular.

Aspecto adicional 24. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de aterosclerosis.

Aspecto adicional 25. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de hipercolesterolemia.

Aspecto adicional 26. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de intensificar el transporte reverso de colesterol.

Aspecto adicional 27. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un

medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de disminuir la absorción de colesterol en el intestino.

Aspecto adicional 28. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de incrementar los niveles de colesterol HDL.

Aspecto adicional 29. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de disminuir los niveles de colesterol LDL.

Aspecto adicional 30. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de afecciones inflamatorias.

Aspecto adicional 31. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de enfermedad de Alzheimer.

Aspecto adicional 32. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de arteriosclerosis.

Aspecto adicional 33. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de diabetes tipo 2.

Aspecto adicional 34. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un

medicamento para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de mejora la función HDL.

Aspecto adicional 35. El uso de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 en la fabricación de un medicamento para el tratamiento y/o profilaxis de trastornos lipídicos (dislipidemia) asociados o no con resistencia a la insulina.

Aspecto adicional 36. Un método de tratar y/o prevenir trastornos lipídicos (dislipidemia) asociados o no con resistencia a la insulina, que comprende la administración de un compuesto de acuerdo con uno cualquiera de los aspectos adicionales 1-18 a un mamífero necesitado de ello.

Aspecto adicional 37. Un método para el tratamiento y/o profilaxis de enfermedad cardiovascular, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 38. Un método de tratar y/o prevenir aterosclerosis que comprende la administración de una cantidad efectiva de un compuesto de fórmula I de acuerdo con uno cualquiera de los aspectos adicionales 1-18 a un mamífero necesitado de ello.

Aspecto adicional 39. Un método para el tratamiento y/o profilaxis de hipercolesterolemia que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 40. Un método para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de intensificar el transporte reverso

de colesterol, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 41. Un método para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de disminuir la absorción de colesterol en el intestino, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 42. Un método para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de incrementar los niveles de colesterol HDL, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 43. Un método para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de disminuir los niveles de colesterol LDL, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 44. Un método para el tratamiento y/o profilaxis de enfermedades inflamatorias, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 45. Un método para el tratamiento y/o profilaxis de enfermedad de Alzheimer, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 46. Un método para el tratamiento y/o profilaxis de arteriosclerosis, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 47. Un método para el tratamiento y/o profilaxis de diabetes tipo 2, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Aspecto adicional 48. Un método para el tratamiento y/o profilaxis de afecciones asociadas con una necesidad de mejorar la función HDL, que comprende administrar a un mamífero, incluido el hombre, necesitado de tal tratamiento, una cantidad efectiva de un compuesto como se define en uno cualquiera de los aspectos adicionales 1-18.

Para los aspectos adicionales 1-48 ya mencionados, se aplicarán las definiciones incluidas más arriba en el texto o las siguientes definiciones:

El término "X" denota un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono en donde dicho grupo alquilo puede interrumpirse opcionalmente por O, S, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2.

El término "Y" denota un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 3 átomos de carbono en donde dicho grupo alquilo se une a nitrógeno en la posición 2 en el 1,1-dióxido de isotiazol-3(2*H*)-ona y puede interrumpirse o terminarse opcionalmente por O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c y/o Y se sustituye opcionalmente por uno o más de los siguientes: OH, F, CN, NR^aR^a, C_1-C_4alquilo, OR^b, SR^b, $S(O)R^b$ o SO_2R^b. En la definición de "Y", el término "interrumpirse por O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c" significa que el grupo alquilo tiene como la última posición O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$ o NR^c antes de que se una adicionalmente a fenilo, heteroarilo, cicloalquilo o heterociclilo.

El término "Z" denota un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono en donde dicho grupo alquilo se une a E o Het^4 y uno de los siguientes: Q, Het^1, R o Het^2, y puede interrumpirse o terminarse opcionalmente por O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, consta opcionalmente sólo de uno de los siguientes: O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a , SO_2NR^a, NR^aSO_2 y/o Z se sustituye opcionalmente por uno o más de los siguientes: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $S(O)R^c$, SO_2R^c, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, el cual se sustituye opcionalmente por uno o más de los siguientes: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b, OR^b. En la definición de "Z", el término "terminarse por O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2" significa que el grupo alquilo tiene como la última posición O, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a o NR^aSO_2 antes de que se una adicionalmente a E, Het^4, Q, Het^1, R o Het^2.

El término "M" denota un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un anillo

bicíclico no aromático o parcialmente aromático, saturado o insaturado, compuesto de 4, 5, 6, 7, 8, 9 ó 10 átomos de carbono.

El término "E" denota un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un anillo bicíclico no aromático o parcialmente aromático, saturado o insaturado, compuesto de 4, 5, 6, 7, 8, 9 ó 10 átomos de carbono. El anillo se une, a menos que se especifique lo contrario, a través de su parte no aromática, a nitrógeno en la posición 4 en el 1,1-dióxido de isotiazol-3(2*H*)-ona.

El término "A" denota un anillo monocíclico aromático, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un anillo bicíclico aromático compuesto de 4, 5, 6, 7, 8, 9 ó 10 átomos de carbono.

El término "P" denota un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono, en donde el grupo alquilo se une a nitrógeno en la posición 4 en el 1,1-dióxido de isotiazol-3(2*H*)-ona y se interrumpe o termina opcionalmente por O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 y/o P se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $S(O)R^b$, SO_2R^b, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, NR^aR^a, SR^b, $S(O)R^b$, SO_2R^b o OR^b. En la definición de "P", el término "se termina por O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2" significa que el grupo alquilo tiene como la última posición O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2" antes de que se una adicionalmente a M, Het^3, A o Het^5.

El término "Q" denota un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7, 8 átomos de carbono, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN,

NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$. Ejemplos de tal Q incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctanilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclopentadienilo, ciclohexadienilo y ciclooctadienilo.

El término "R" denota un grupo fenilo, que se sustituye opcionalmente por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

El término "T" denota un grupo alquilo con 1 átomo de carbono o, de manera opcional, consiste de uno o más de los siguientes: O, NR^a, S, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2. T se une a M, Het^3, A o Het^5.

El término "C_1alquilo" denota un grupo alquilo con 1 átomo de carbono. Un ejemplo de dicho alquilo incluye, pero no se limita a, metilo.

El término "C_1-C_3alquilo" denotes un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 3 átomos de carbono.

El término "C_1-C_4alquilo" denota un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 4 átomos de carbono.

El término "cicloalquilo" denota un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7, 8 átomos de carbono, e incluye, pero no se limita a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctanilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclopentadienilo, ciclohexadienilo y ciclooctadienilo.

El término "heterociclilo" denota un anillo monocíclico, de 3-8 miembros, no aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre. Se entenderá que el término "azufre" incluye sulfóxido (S(O)) y sulfona (SO_2). Se entenderá que el término "nitrógeno" incluye óxido de nitrógeno (NO).

El término "heteroarilo" denota un anillo monocíclico, de 3-8 miembros, aromático, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno y azufre. Se entenderá que el término "azufre" incluye sulfóxido (S(O)) y sulfona (SO_2). Se entenderá que el término "nitrógeno" incluye óxido de nitrógeno (NO).

El término "Het^1" denota un anillo monocíclico de 3-10 miembros, no aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, y en donde el anillo se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$,

$C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$. Se entenderá que el término "azufre" incluye sulfóxido (S(O)) y sulfona (SO_2). Se entenderá que el término "nitrógeno" incluye óxido de nitrógeno (NO).

El término "Het^2" denota un anillo monocíclico de 3-10 miembros, aromático, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno y azufre, y el cual se sustituye por uno o más de los siguientes: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes: F, OH, CN, NR^aR^a, OR^b, SR^b, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$. Se entenderá que el término "azufre" incluye sulfóxido (S(O)) y sulfona (SO_2). Se entenderá que el término "nitrógeno" incluye óxido de nitrógeno (NO).

El término "Het^3" denotes un anillo monocíclico de 3-10 miembros, no aromático, saturado o insaturado o un anillo bicíclico de 4-10 miembros, no aromático o parcialmente aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo monocíclico o bicíclico es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre. Se entenderá que el término "azufre" incluye sulfóxido (S(O)) y sulfona (SO_2). Se entenderá que el término "nitrógeno" incluye óxido de nitrógeno (NO).

El término "Het^4" denota un anillo monocíclico de 3-10 miembros, no aromático, saturado o insaturado o un anillo bicíclico de 4-10 miembros, no aromático o parcialmente aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo monocíclico o bicíclico es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre. Se entenderá

que el término "azufre" incluye sulfóxido (S(O)) y sulfona (SO_2). Se entenderá que el término "nitrógeno" incluye óxido de nitrógeno (NO). El anillo se une, a menos que se especifique lo contrario, a través de su parte no aromática, a nitrógeno en la posición 4 en el 1,1-dióxido de isotiazol-3(2*H*)-ona.

El término "Het^5" denota un anillo monocíclico de 3-10 miembros, aromático o un anillo bicíclico de 4-10 miembros, aromático en el cual uno o más de los átomos en el anillo monocíclico o bicíclico es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre. Se entenderá que el término "azufre" incluye sulfóxido (S(O)) y sulfona (SO_2). Se entenderá que el término "nitrógeno" incluye óxido de nitrógeno (NO).

R^a representa independientemente H o una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.
R^b representa independientemente una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.
R^c representa independientemente H o una cadena C_1-C_3alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.

La invención se ilustra por los siguientes Ejemplos, pero no se limita a ellos.

La denominación de los compuestos en esta solicitud de patente se hizo o bien usando un programa de ACD Labs (version 6.0/Name, 6.0 Name Batch o labs 8.0/Name) o bien usando la función Autonom 2000 Name en el programa Isis Draw.

Ejemplos

Abreviaturas

AcOH ácido acético

Atm	atmósfera
DBU	2,3,4,6,7,8,9,10-octahidropirimido[1,2-α]azepina
DCM	diclorometano
DIPEA	*N*,*N*-diisopropiletilamina
DMAP	4-dimetilaminopiridina
DMF	*N*,*N*-dimetilformamida
DMSO	sulfóxido de dimetilo
EDC	clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida
Et_2O	éter dietílico
EtOAc	acetato de etilo
EtOH	etanol
HOAt	1-hidroxi-7-azabenzotriazol
HOBt	1*H*-1,2,3-benzotriazol-1-ol
HPFC	cromatografía rápida de alta resolución
HPLC	cromatografía líquida de alta resolución
LC-MS	cromatografía líquida – espectrometría de masa
MeCN	acetonitrilo
MCPBA	ácido metacloroperbenzoico
MeOH	metanol
MTBE	metil *terc*-butil éter
NMR	nuclear magnetic resonance
PyBOP	hexafluorofosfato de benzotriazol-1-il-oxitripirrolidinofosfonio
TEA	trietilamina
TFA	ácido trifluoroacético
THF	tetrahidrofuran
UV	ultravioleta
rt	temperatura de la sala
h	hora(s)
mins	minutos
b	amplio
bs	singlete amplio
d	dublete

dd	doble doblete
m	multiplete
qt	quintete
s	singlete
t	triplete
hep	heptete
ds	doble singlete
sep	septete

Procedimientos Experimentales de Ejemplos Generales

Se utilizó un Separador de Fases de IST. ISOLUTE SCX-2 se usaron como columnas de intercambio iónico. La cromatografía rápida en columna empleó gel de sílice de fase normal 60 (0.040-0.063 mm, Merck) o las columnas IST Isolute®SPE emplearon gel de sílice de fase normal o Sistema HPFC Biotage Horizon o un sistema rápido Horizon TM usando cartuchos FLASH+ HPFC en sílice. Las purificaciones por HPLC se llevaron a cabo o bien en un sistema Gilson de HPLC preparativa con un colector de fracción disparado por UV, equipado con una columna ACE C8 5 μm 250 mm x 20 mm, o una columna Kromasil C18, o bien en un sistema de HPLC preparativa Waters, equipado con una columna Kromasil C8 10 μm 250 mm x 21.2 mm, o en un sistema de HPLC preparativa Waters, equipado con una columna ACE C8 5 μm 250 mm x 50 mm o una columna ACE C8 5 μm 250 mm x 20 mm, o en un sistema HPLC FractionLynx Waters con un colector de fracciones disparado por masa, equipado con una columna ACE C8 5μm 100 mm x 21.2 mm; usando un sistema amortiguador MeCNZNH$_4$OAc con una gradiente de 100% fase móvil A (5% MeCN + 95% 0.1 M NH$_4$OAc) a 100% fase móvil B (100% MeCN), a menos que se indique lo contrario. Las mediciones ^{1}H NMR y ^{13}C NMR se realizaron en un espectrómetro BRUKER ACP 300 o en un Varian Unity Plus 400, 500 ó 600, que operaban con frecuencias ^{1}H de 300, 400, 500, 600 MHz, respectivamente, y frecuencias ^{13}C de 75, 100, 125 y 150 MHz, respectivamente. Los deplazamientos químicos se dan en valores δ (ppm)

con los disolventes usados como estándar interno, a menos que se indique lo contrario. El calentamiento con microondas se efectuó usando calefacción de nodo simple en un Optimizador Creator o Emrys de Personal Chemistry, Uppsala, Suecia. Los datos de los espectros de masa se obtuvieron usando un microsistema Micromass LCT o Waters Q-Tof y, donde se consideró apropiado, se recolectaron datos de iones positivos o datos de iones negativos.

Los N-óxidos de piridina se prepararon oxidando los correspondientes compuestos de piridina con un agente oxidante, tal como ácido metacloroperbenzoico (MCPBA) en un disolvente orgánico inerte tal como DCM a temperatura de la sala durante 2-24 horas.

Síntesis

Material de Partida e Intermedios

N-(*terc*-Butil)-1-fenilmetanosulfonamida

El compuesto del título se preparó como se describe en la siguiente referencia:

Org. Biomol. Chem., 2003, 19, 3390-3395

1,1-Dióxido de 2-*terc*-butil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona

terc-Butóxido de potasio (0.845g, 10.56mmol) se agregó a una solución de N-(*terc*-butil)-1-fenilmetanosulfonamida (1.2g, 5.28mmol) y oxalato de dietilo (0.85mL, 6.33mmol) en THF (8mL) y la mezcla se calentó a 150°C durante 15 minutos en un reactor microondas. La mezcla de reacción se acidificó con 1M HCl, el THF se evaporó y el residuo se extrajo con DCM. La evaporación y trituración del residuo con éter de petróleo produjeron el compuesto del título (7g, 63%) como un sólido; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.32 (m, 5H), 3.90 (br s, 1H), 1.36 (s, 9H); Espectro de Masa: M-H$^+$ 280

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona

Cloruro de oxalilo (3.39g, 2.71mmol) se agregó gota a gota a una solución de 1,1-dióxido de 2-*terc*-butil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona (5g, 17.77mol) y DMF (15mL) en DCM (220mL) a 0°C. La mezcla de reacción

se calentó a 50°C durante 4 horas, se concentró y el residuo se diluyó con EtOAc y se lavó con agua, luego salmuera y se evaporó. El residuo se purificó por cromatografía en columna de gel de sílice, usando una mezcla 98:2 de éter de petróleo y EtOAc como eluyente. El producto que contenía las fracciones se evaporó, el residuo se trituró en éter de petróleo y el disolvente se decantó para producir el compuesto del título (3.9g, 74%) como un sólido; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.92 (m, 2H), 7.61-7.51 (m, 3H), 1.75 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 142.8, 132.3, 129.3, 128.8, 123.4, 63.0, 27.7.

1,1-Dióxido de 4-[(3-bromopropil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

Una solución de TEA (0.18mL, 1.33mmol) en MeCN (5mL) se agregó gota a gota a una mezcla de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.20g, 0.67mmol) e hidrobromuro de (3-bromopropil)amina (0.146g, 0.67mmol) en MeCN (3mL). Luego de 45 minutos, una solución de hidrobromuro de (3-bromopropil)amina (0.073g, 0.33mmol) y TEA (0.093mL, 0.66mmol) en MeCN (5mL) se agregó gota a gota a la mezcla de reacción. Luego de 3 horas, hirobromuro de (3-bromopropil)amina (0.073g, 0.33mmol) y TEA (0.093mL, 0.66mmol) se agregaron a la mezcla de reacción. Luego de 17 horas el disolvente se evaporó y el residuo se purificó por cromatografía en columna de gel de sílice usando 10-20% EtOAc en mezcla de éter de petróleo como eluyente, para proporcionar el compuesto del título (0.112g, 42%) como un sólido; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.50 (m, 2H), 7.50-7.44 (m, 3H), 5.32 (t, 1H), 3.18 (t, 3H), 3.10-3.04 (m, 2H), 1.90-1.78 (m, 2H), 1.76 (s, 9H); Espectro de Masa $M+H^+$ 403.

***N*-Butil-1-fenilmetanosulfonamida**

El compuesto del título puede prepararse como se describe en la siguiente referencia: Heterocycles, 1993, 36(4), 733-742

1,1-Dióxido de 2-butil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona

N-Butil-1-fenilmetanosulfonamida (2.0g, 8.80mmol) se disolvió en DMF seco (13mL) bajo una atmósfera de nitrógeno. Oxalato de dietilo (1.44g,

9.83mmol) se agregó y la mezcla de reacción se enfrió a 0°C usando un baño helado. *terc*-Butóxido de potasio (1.25g, 11.14mmol) se agregó en una porción y la mezcla de reacción se agitó durante 5 minutos a 0°C, seguidos por 19 horas a temperatura de la sala. La mezcla se enfrió en un baño helado, y HCl (2M) se agregó cuidadosamente para dar un pH~1 de la mezcla. La mayoría de los disolventes se evaporaron y el residuo se repartió en porciones entre HCl (2M) y EtOAc. Las capas orgánicas combinadas se lavaron con agua varias veces, se secaron con $MgSO_4$ y se evaporaron a sequedad. El residuo se purificó usando HPLC preparativa (ACE C8, 0.1M NH4OAc/MeCN, gradiente) para producir el compuesto del título (0.96 g, 39%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88-7.83 (m, 2H), 7.22-7.29 (m, 3H), 7.14 (bs, 1H), 6.98-7.15 (m, 2H), 3.48 (t, 2H), 1.59-1.67 (m, 2H), 1.27-1.37 (m, 2H), 0.88 (t, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 158.4, 132.3, 128.7, 124.2, 123.2, 37.8, 30.9, 20.2, 14.1; Espectro de Masa: M-H$^+$ 280.

1,1-Dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-butil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona (444mg, 1.58mmol) se disolvió en DCM seco (15mL) a temperatura de la sala y bajo una atmósfera de nitrógeno. Cloruro de oxalilo (0.15mL, 1.73mmol) se agregó gota a gota y la mezcla de reacción se hizo refluir durante 1.5 horas. DMF (0.08mL) se agregó seguido por la adición de cloruro de oxalilo (0.15mL, 1.73mmol) en 2 porciones y la mezcla de reacción se hizo refluir durante otras 6 horas. Los disolventes se evaporaron y el residuo se repartió en porciones entre agua y DCM. Las capas orgánicas combinadas se lavaron con agua y las dos fases se separaron usando un separador de fases. La evaporación de la fase orgánica produjo el compuesto del título (440mg, 88%) como un aceite marrón con aproximadamente 95% de pureza de acuerdo con ^{1}H-NMR y se utilizó sin purificación posterior; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96-8.00 (m, 2H), 7.53-7.62 (m, 3H), 3.74-3.80 (t, 2H), 1.78- 1.87 (m, 2H), 1.39-1-50 (m, 2H), 0.98 (t, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.3, 137.1, 132.7, 129.6, 129.2, 127.6, 123.7, 40.9, 30.1, 20.1, 13.7.

N-Isopropil-1-fenilmetanosulfonamida

El compuesto del título puede prepararse como se describe en la siguiente referencia:

Orazi, Orfeo O.; Corral, Renee A.; Bravo, Rodolfo; J. Heterocycl.Chem.; 23; 1986; 1701-1708.

1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

Paso A. **Metil[(bencilsulfonil)(isopropil)amino](oxo)acetato**

Una mezcla de N-isopropil-1-fenilmetanosulfonamida (1.0g, 4.7mmol) y cloruro de metil oxalilo (2.0 mL, 21,6 mmol) se calentó a 120°C durante 1 hora. La evaporación produjo metil[(bencilsulfonil)(isopropil)amino](oxo) acetate, el cual se utilizó directamente en la siguiente reacción sin ninguna purificación.

Paso B. **1,1-Dióxido de 4-hidroxi-2-isopropil-5-fenilisotiazol-3(2*H*)-ona**

terc-Butóxido de potasio (1.5g, 13.4mmol) se agregó a una solución de metil[(bencilsulfonil)(isopropil)amino](oxo)acetato crudo (2.0g, 21.6mmol) en DMF (15mL). Luego de 17 horas, la mezcla se evaporó y el residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 4:1 de EtOAc y MeOH como eluyente, para producir el compuesto del título (0.5g, 40%) como un sólido.

Paso C **1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona**

DMF (25mL) y cloruro de oxalilo (0.2mL, 2.29mmol) se agregaron separadamente a una solución de 1,1-dióxido de 4-hidroxi-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.5g, 1.87mmol) en DCM (25mL) a 0 °C. La mezcla de reacción se calentó entonces a 50°C durante 4 horas, se agregó agua y la mezcla resultante se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua, luego salmuera y se evaporaron. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 4:1 de hexano y EtOAc como eluyente para producir el compuesto del título (0.25g, 46 %) como un sólido; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10-7.94 (m, 2H), 7.61- 7.50 (m, 3H), 4.50 (sep, 1H), 1.61 (s, 3H), 1.65 (s, 6H).

2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil 4-metilbencenosulfonato

El compuesto del título se preparó como se describe para 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato de 1,1-dióxido de 2-*terc*-butil-4-[(2-hidroxietil) amino]-5-fenilisotiazol-3(2*H*)-ona (Ejemplo 76) y cloruro de 4-metilbencenosulfonilo con un tiempo de reacción de 17 horas. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 50-100% DCM en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (1.93g, 76%) como un sólido; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.76 (d, 1H), 7.46-7.35 (m, 7H), 5.44 (t, 1H), 3.85 (t, 2H), 3.18- 3.12 (m, 2H), 2.49 (s, 3H), 1.74 (s, 9H); Espectro de Masa $M+H^+$ 479.

1,1-Dióxido de 2-*terc*-butil-4-[(3-cloropropil)amino]-5-fenilisotiazol-3(2*H*)-ona

Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-[(3-hidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona (Ejemplo 49) (0.14g, 0.42mmol), cloruro de 4-metilbencenosulfonilo (0.089mg, 0.46mmol) y TEA (0.065ml, 0.46mmol) en DCM (2ml) se agitó a temperatura de la sala durante 2 horas, luego de las cuales se agregaron TEA (0.065ml, 0.46mmol) y cat. DMAP. Luego de 18 horas se agregaron más cloruro de 4-metilbencenosulfonilo (0.16mg, 0.84mmol), TEA (0.059ml, 0.42mmol) y DMAP (0.052g, 0.42mmol). Luego de 5 horas la mezcla de reacción se calentó a reflujo durante 18 horas y se evaporó a sequedad. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 10% EtOAc en hexano como eluyente para producir el compuesto del título (0.097g, 64%). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.50-7.44 (m, 3H), 5.32 (t, 1H), 3.35 (t, 2H), 3.08 (q, 2H), 1.80-1.72 (m, 11H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.8, 135.0, 131.8, 130.0, 128.9, 124.9, 107.8, 61.8, 41.7, 41.3, 32.0, 27.8; Espectro de Masa: $M+H^+$ 357.

3-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propil 4-metilbencenosulfonato

Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-[(3-hidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona (Ejemplo 49) (2.75g, 8.12mmol), cloruro de 4-metilbencenosulfonilo (1.86g, 9.74mmol), DMAP (0.99g, 8.12mmol) y Na_2CO_3 (2.58g, 24.35mmol) en DCM (50ml) se agitó a temperatura de la sala. Luego de 2 horas, la mezcla se filtró, se evaporó y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 5:1 DCM/éter de petróleo 40-60°C como eluyente para producir el compuesto del título (2.34g, 58%) como un sólido; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.74 (d, 2H), 7.50-7.39 (m, 3H), 7.36 (d, 2H), 5.30 (t, 1H), 3.85 (t, 2H), 2.98 (q, 2H), 2.48 (s, 3H), 1.73 (s, 9H), 1.62 (qt, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.8, 145.4, 134.9, 132.9, 131.8, 130.2, 130.1, 129.0, 128.1, 124.9, 107.9, 67.2, 61.6, 40.3, 28.8, 27.8, 21.9; Espectro de Masa $M+H^+$ 493.

1,1-Dióxido de 4-[(2-hidroxietil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (1.10g, 3.85mmol) se disolvió en DMF seco (10mL) bajo una atmósfera de nitrógeno. 2-Aminoetanol (0.28g, 4.62mmol) se agregó seguido por TEA (0.58g, 5.77mmol). La mezcla de reacción se calentó en un reactor microondas a 120°C durante 15 minutos. La mezcla se diluyó con EtOAc, se lavó con $NaHCO_3$ acuoso saturado, se secó con Na_2SO_4, se filtró y se evaporó. El residuo se purificó en un sistema HPFC Biotage Horizon usando heptano y EtOAc como eluyente y TEA como aditivo, lo cual proporcionó el compuesto del título (1.18g, 99.1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, 6H), 3.02 (q, 2H), 3.57 (t, 2H), 4.38-4.46 (m, 1H), 5.71 (bs, 1H), 7.43-7.46 (m, 3H), 7.50-7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.38, 46.11, 47.76, 60.78, 107.46, 125.22, 128.96, 129.89, 131.70, 135.84, 158.67; Espectro de Masa: $M+H^+$ 311.

2-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil 4-metilbencenosulfonato

Una mezcla de 1,1-dióxido de 4-[(2-hidroxietil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (1.10g, 3.54mmol), cloruro de 4-toluenosulfonilo (0.81g, 4.25mmol), DMAP (0.43g, 3.54mmol) y Na_2CO_3 (1.13g, 10.63mmol) en DCM seco (20mL) se agitó a temperatura de la sala durante 4 horas. La mezcla se filtró y se concentró. El producto crudo se purificó en un sistema rápido Horizon TM f usando heptano y EtOAc como eluyente y TEA como aditivo, lo cual proporcionó el compuesto del título (1.17g, 71.1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, 6H), 2.48 (s, 3H), 3.18 (q, 2H), 3.85 (t, 2H), 4.37-4.45 (m, 1H), 5.47 (t, 1H), 7.37 (d, 2H), 7.40-7.46 (m, 5H), 7.76 (d, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.37, 21.95, 42.80, 47.91, 67.46, 108.77, 124.61, 128.17, 129.19, 130.27, 130.32, 131.54, 132.48, 135.00, 145.74, 158.21; Espectro de Masa: $M+H^+$ 465.

1,1-Dióxido de 4-[(2-aminoetil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

Etilendiamina (0.60g, 10.0mmol) se disolvió en DMF seco (50 ml) y se calentó a 60°C. 1,1-Dióxido de 2-*terc*-Butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (1.00 g, 3.34mmol) disuelto en DMF (10 ml) se agregó gota a gota durante 30 minutos y se agitó a 60°C durante 10 minutos. La mezcla de reacción se diluyó con EtOAc (300 ml) y se lavó con agua (400 ml y 2x200ml), se secó (Na_2SO_4), se filtró y se evaporó para producir el compuesto del título (0.97g, 90%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H), 7.42-7.37 (m, 3H), 5.83-5.76 (m, 1H), 2.84-2.78 (m, 2H), 2.67-2.62 (m, 2H), 1.71 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.7, 135.4, 131.6, 129.5, 128.6, 125.2, 106.9, 61.5, 46.2, 40.8, 27.7; Espectro de Masa: $M+H^+$ 324.

1,1-Dióxido de 4-[(4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.15g, 0.53 mmol), 4-aminociclohexanol (0.092g, 0.80 mmol) y TEA (0.081g, 0.80 mmol) se disolvió en MeCN seco (3 ml). La reacción se calentó en un

reactor microondas a 120°C durante 10 minutos. Se agregaron unas cuantas gotas más de 4-aminociclohexanol y la reacción se calentó en un reactor microondas a 140°C durante 20 minutos. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 25:75 de hexano y EtOAc, para producir una mezcla 50:50 de *cis* y *trans* isómeros (0.130g, 67%). La mezcla se separó por HPLC (C8, 0.05M NH4OAc (pH=4.1):MeCN 1:1) para producir cis (Ejemplo 38) y trans (Ejemplo 48) isómeros.

_N_-(2-Metoxietil)-1-fenilmetanosulfonamida

Cloruro de fenilmetanosulfonilo (3.0g, 15.7mmol) se disolvió en THF seco (15mL) y se agregó gota a gota a una solución de 2-metoxietilamina (2.36g, 31.5mmol) en THF seco (50mL) a 0°C. Luego de la adición, se retiró el baño helado y la reacción se agitó a temperatura de la sala durante 2.5 horas. El disolvente se retiró *in vacuo* y el residuo se disolvió en DCM. La mezcla se lavó con una porción de 5% de HCl acuoso, varias porciones de agua, se secó a través de un separador de fases y se evaporó para producir el compuesto del título (3.58g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.35 (m, 5H), 4.52 (br s, 1H), 4.26 (s, 2H), 3.40 (t, 2H), 3.32 (s, 3H), 3.14-3.09 (m, 2H); Espectro de Masa: M-H$^+$ 228.

1,1-Dióxido de 4-hidroxi-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

Una solución de N-(2-metoxietil)-1-fenilmetanosulfonamida (3.5 g, 14.5 mmol) y oxalato de dietilo (2.33g, 16.0mmol) en DMF seco se enfrió en un baño helado. Se agregó *terc*-butóxido de potasio (2.17g, 18.4mmol) y, luego de 5 minutos, se retiró el baño helado y la reacción se agitó a temperatura de la sala durante 22 horas. 2M HCl (45mL) se agregó a la mezcla y la solución ácida se extrajo 3 veces con diclorometano. Las capas orgánicas combinadas se lavaron 4 veces con agua, se secaron a través de un separador de fases y se evaporaron. El residuo se purificó por HPLC preparativa [0.1M NH_4OAc/MeCN, (9:1 a 1:9)] para producir el compuesto del título (0.250 g, 6%) como un sólido; ^{1}H NMR (500 MHz, CD_3OD): δ 7.90-7.94 (m, 2H), 7.28-7.33 (m, 2H), 7.10-7.15 (m, 1H), 3.79 (t, 2H), 3.68 (t, 2H), 3.34 (s, 3H); Espectro de Masa: M-H$^+$ 282.

1,1-Dióxido de 4-cloro-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

Cloruro de oxalilo (0.185g, 1.46mmol) se agregó gota a gota a una solución de 1,1-dióxido de 4-hidroxi-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona (0.250g, 0.88mmol) en DCM (15 mL). La mezcla se hizo refluir durante 2 días y luego se evaporó. El residuo se disolvió en agua y se extrajo 3 veces con diclorometano. Las capas orgánicas combinadas se lavaron 2 veces con agua, se secaron a través de un separador de fases y se evaporaron para producir el compuesto del título (0.245g, 92%) como un sólido; ^{1}H NMR (500 MHz, CD_3OD): δ 7.94-7.97 (m, 2H), 7.58-7.67 (m, 25 3H), 3.94 (t, 2H), 3.70 (t, 2H), 3.38 (s, 3H).

N-Etil-1-fenilmetanosulfonamida

El compuesto del título se preparó como se describe en la siguiente referencia:

Orazi, Orfeo O.; Corral, Renee A.; Bravo, Rodolfo; J. Heterocycl. Chem.; 23; 1986; 1701-1708.

1,1-Dióxido de 2-etil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona

N-Etil-1-fenilmetanosulfonamida (20g) se dividió en lotes de 0.5g cada uno y se tomó en un frasquito de 8mL. A cada frasquito se agregó *terc*-butóxido de potasio (0.426g, 3.8mmol), oxalato de etilo (0.408mL, 3.01mmol) y THF seco (4mL). Cada frasquito se calentó en un reactor microondas a 145°C durante 20 minutos. Las mezclas de reacción de todos los frasquitos se combinaron y se trataron con 1.5 N HCl (75mL) y se extrajeron con EtOAc. Las capas orgánicas se lavaron con agua (3 x 25mL) y salmuera, se secaron sobre Na_2SO_4 y se evaporaron. Una pequeña cantidad del DCM se agregó al residuo sólido y se agitó bien. La filtración produjo el compuesto del título casi puro (21g, 82.6%) como un sólido blancuzco; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, 3H, J = 7.2 Hz), 3.8 (q, 2H, J = 7.2 Hz), 7.3-7.5 (m, 3H), 7.9 - 8.0 (m, 2H).

1,1-Dióxido de 4-cloro-2-etil-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-etil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona (5g, 19.76mmol) se disolvió en DCM seco (250mL) y se enfrió a 0°C bajo N_2. Se agregó DMF seco (15mL), seguido por cloruro de oxalilo (3mL, 34.4mmol). El

baño helado se retiró y la mezcla se hizo refluir a 50°C bajo N_2 durante 4 horas. La mezcla de reacción se evaporó y el residuo se diluyó con EtOAc, se lavó con agua (3 x 25mL) y salmuera, se secó sobre Na_2SO_4 y se evaporó. Otra porción (16g, 63.24mmol) de 1,1-dióxido de 2-etil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona se disolvió en DCM seco (500mL) y se enfrió a 0°C bajo N_2. Se agregó DMF seco (20mL), seguido por cloruro de oxalilo (9 mL, 103.2 mmol). El baño helado se retiró y la mezcla se hizo refluir a 50°C bajo N_2 durante 4 horas. La mezcla de reacción se evaporó y el residuo se diluyó con EtOAc, se lavó con agua (3 x 50mL) y salmuera, se secó sobre Na_2SO_4 y se evaporó, con lo cual se obtuvo un sólido rojo. El material crudo de ambos lotes se combinó y se purificó por cromatografía en columna en gel de sílice usando 2.5-3 % etil acetato en éter de petróleo como eluyente, y se recristalizó de metanol para producir el compuesto del título (15.7g, 70%) como un sólido blanco; ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (t, 3H, J = 7.3 Hz), 3.84 (q, 2H, J = 7.3 Hz), 7.6 - 7.7 (m, 3H), 7.9 - 8.0 (m, 2H); Espectro de Masa: $M+H^+$ 272.

Metil 4-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoato

El compuesto del título se preparó como se describe para Ejemplo 5 de 1,1-dióxido de 2-*terc*-butil-4-[(3-bromopropil)amino]-5-fenilisotiazol-3(2*H*)-ona y metil 3-hidroxibenzoato a una temperatura de 100°C. El residuo se purificó por cromatografía rápida usando hexano y EtOAc como eluyente para producir el compuesto del título (0.124g, 49%).

4-{2-[1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil} fenil metanosulfonato

Una mezcla de 4-{2-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}fenil metanosulfonato (Ejemplo 77) (0.160g, 0.334mmol) en TFA (1ml) se calentó en un reactor microondas a 120°C durante 25 minutos. La mezcla de reacción se evaporó a sequedad y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 6-12% MeOH en EtOAc (+1% AcOH) como eluyente para producir el compuesto del título (0.047g, 43%) como un

sólido; ^{1}H NMR (500MHz CD_3OD): δ 7.54-7.47 (m, 5H), 7.13 (d, 2H), 6.84 (d, 2H), 3.20-3.14 (m, 5H), 2.56 (t, 2H); ^{13}C NMR (125MHz CD_3OD): δ 164.2, 148.4, 137.9, 136.7, 131.5, 130.1, 129.1, 128.5, 127.1, 121.9, 108.2, 44.4, 36.2, 34.9; Espectro de Masa: $M+H^+$ 423

Metil [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]acetato

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (1.09g, 3.64mmol), clorhidrato de metil glicinato (0.68g, 5.46mmol) y TEA (1.10g, 10.92mmol) se disolvieron en una mezcla de MeCN (10mL) y DMF (5mL), y la mezcla de reacción se agitó a 65 °C de un día para otro. La mezcla de reacción se evaporó y el residuo se diluyó con $NaHCO_3$ acuoso saturado y la mezcla se extrajo con DCM. Las fases orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron y se evaporaron para producir el compuesto del título.

Ácido [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]acético

Metil [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]acetato (1.28g, 3.64mmol) se dispersó en una mezcla de dioxano (20mL), MeOH (20mL) y agua (20mL). Se agregó LiOH acuoso (1M, 0.218g, 9.10 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 2 horas. Se agregó cuidadosamente HCl acuoso a la mezcla de reacción para dar el pH~1 y la mezcla resultante se extrajo con DCM. Las fases orgánicas se combinaron, se secaron sobre $Na2SO_4$, se filtraron, se evaporaron, y el residuo crudo se purificó por HPLC preparativa, produciendo el compuesto del título (0.51g, 41%). ^{1}H-NMR (CD_3OD, 500 MHz): δ 7.52-7.48 (m, 2H), 7.46-7.42 (m, 3H), 5.41 (brs, 8H) 1.95 (s, 2H), 1.71 (s, 9H); ^{13}C-NMR (CD_3OD, 125 MHz): δ 178.4, 174.8, 160.8, 136.5, 132.8, 130.4, 129.5, 126.6, 107.4, 62.1, 48.3, 27.9, 22.9.

***terc*-Butil [1-(2-cianoetil)piperidin-4-il]carbamato**

3-Bromopropionitrilo (0.74g, 5.49mmol) se agregó a una solución de *terc*-butil piperidin-4-ilcarbamato (1.00g, 4.99mmol) y TEA (0.56 g, 5.49mmol) en MeCN (15mL), y la mezcla se calentó a 60°C durante 5 horas y luego se

evaporó. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando una mezcla 40:60 y luego una mezcla 15:85-10:90 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.40g, 32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.44 (br s, 1H), 3.54-3.42 (br m, 1H), 2.88-2.79 (m 2H), 2.69 (t, 2H), 2.51 (t 2H), 2.24-2.16 (m, 2H), 1.99-1.92 (m 2H), 1.47 (s 9H), 1.49-1.41 (m 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 119.0, 53.6, 52.2, 47.7, 32.7, 28.6, 16.4.

3-(4-Aminopiperidin-1-il)propanonitrilo

TFA (1.21g, 10.62mmol) se agregó a una solución de *terc*-butil [1-(2-cianoetil)piperidin-4-il]carbamato (0.27g, 1.06mmol) en DCM (11mL), y la mezcla se agitó a temperatura de la sala durante 2 horas. La mezcla se evaporó y el producto se utilizó sin purificación posterior de ninguna clase.

2-(4-Fenoxibutil)-1*H*-isoindol-1,3(2*H*)-diona

Una mezcla de N-(4-bromobutil)ftalimida) (2.00g, 7.09mmol), fenol (0.67g, 7.09) y K_2CO_3 (1.96g, 14.18mmoml) en MeCN seco (30ml) se agitó a temperatura de la sala durante 66 horas. La mezcla de reacción se calentó entonces a 50°C durante 20 horas antes de que se agregara más fenol (0.33mg, 3.54mmol), y la mezcla resultante se calentó a reflujo. Luego de 4 horas, se agregó EtOAc, la mezcla se lavó con salmuera, a continuación 1N NaOH, y salmuera nuevamente antes de evaporar la fase orgánica a sequedad para producir el compuesto del título (1.11g, 53%), el cual se utilizó sin purificación posterior. ^{1}H NMR (500MHz $CDCl_3$): δ 7-90-7.83 (m, 2H), 7.76-7.70 (m, 2H), 7.28 (t, 2H), 6.93 (t, 1H), 6.89 (d, 2H), 4.01 (t, 2H), 3.79 (t, 2H), 1.96-1.82 (m, 4H); Espectro de Masa: $M+H^+$ 296.

(4-Fenoxibutil)amina

Una mezcla de 2-(4-fenoxibutil)1*H*-isoindol-1,3(2*H*)-diona (1.10g, 3.27mmol) y 25% de solución de hidracina en agua (2.88ml, 13.10mmol) en EtOH (30ml) se calentó a reflujo. Luego de 1.5 horas, se agregó EtOAc y la mezcla se extrajo con salmuera. Las fases acuosas combinadas se re-extrajeron entonces con EtOAc y se combinaron todas las fases orgánicas. Éstas se extrajeron luego con 1N HCl, se combinaron las fases acuosas ácidas, se basificaron con 2N NaOH y se re-extrajeron en EtOAc antes de

evaporar a sequedad para producir el compuesto del título (0.411mg, 67%) como un aceite. ^{1}H NMR (500MHz $CDCl_3$): δ 7.32-2.26 (m, 2H), 6.95 (t, 1H), 4.00 (t, 2H), 2.80 (t, 2H), 1.90-1.82 (m, 2H), 1.68-1.62 (m, 2H).

terc-Butil [2-(4-hidroxifenil)etil]carbamato

4-(2-Aminoetil)fenol (2.00g, 14.58mmol) se disolvió en THF (70mL) y MeOH (10mL), y se agregó TEA (1.47g, 14.58mmol). La mezcla se enfrió en un baño helado. Di-_terc_-butil dicarbonato (3.18g, 14.58mmol) se agregó. La mezcla se agitó durante 1 hora a 0°C y se dejó a temperatura de la sala de un día para otro. El disolvente se evaporó y cromatografía en columna del producto crudo (ISOLUTE SI, (20g), eluida con Heptano/EtOAc (90:10), Heptano/EtOAc (70:30)) produjo el compuesto del título (3.47g, 100%). ^{1}H NMR (500MHz, CD_3OD): δ 1.43 (s, 9H), 2.66 (t, 2H), 3.20 (t, 2H), 6.72 (d, 2H), 7.02 (d, 2H); Espectro de Masa: M-H$^+$ 236.

4-{2-[(_terc_-Butoxicarbonil)amino]etil}fenil metanosulfonato

terc-Butil [2-(4-hidroxifenil)etil]carbamato (3.45g, 14.54mmol) se disolvió en DCM seco (70mL) y se enfrió en un baño helado. Se agregó cloruro de metanosulfonilo (1.99g, 17.45mmol), seguido por TEA (2.21g, 21.80mmol). La mezcla de reacción se agitó a temperatura de la sala durante 2 horas. La mezcla de reacción se lavó con $NaHCO_3$ acuoso saturado, y la fase orgánica se secó con $MgSO_4$, se filtró y se evaporó. Cromatografía en columna del producto crudo (ISOLUTE SI, (20g), eluida con Heptano/EtOAc (90:10), Heptano/EtOAc (70:30)) produjo el compuesto del título (4.06g, 88.5%). ^{1}H NMR (500MHz, CD_3OD): δ 1.43 (s, 9H), 2.80 (t, 2H), 3.20 (s, 3H), 3.29 (q, 2H), 7.25 (d, 2H), 7.31 (d, 2H).

4- (2- Aminoetil)fenil metanosulfonato

4-{2-[(_terc_-Butoxicarbonil)amino]etil}fenil metanosulfonato (3.98g, 12.62mmol) se disolvió en DCM (12mL) y TFA (10mL) y se agitó a temperatura de la sala durante 4 horas. La mezcla de reacción se concentró y se re-disolvió en EtOAc, se lavó con K_2CO_3 acuoso saturado, y la fase orgánica se secó con Na_2SO_4, se filtró y se evaporó, lo cual proporcionó el compuesto del título (2.71g, 99.8%). ^{1}H NMR (500MHz, CD_3OD): δ 2.79 (t, 2H), 2.89 (t, 2H), 3.21 (s, 3H), 7.26 (d, 2H), 7.32 (d, 2H); ^{13}C NMR

(125MHz, CD_3OD): δ 36.24, 38.34, 42.95, 122.11, 130.19, 30 139.44, 148.28; Espectro de Masa: $M+H^+$ 216.

terc-Butil 3-(2-amino-2-oxoetil)azetidin-1-carboxilato

PyBOP (1.946g, 3.74mmol) se agregó a una solución de ácido [1-(_terc_-butoxicarbonil)azetidin-3-il]acético (0.805g, 3.74 mmol) en DMF (10mL). La mezcla se agitó en un baño helado, se hizo burbujear gas de amoníaco durante 3 minutos, y luego la mezcla se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se concentró, se agregaron agua (15mL) y $NaHCO_3$ acuoso saturado (5mL), y la mezcla se extrajo con EtOAc (20mLx3). Los extractos se combinaron, se lavaron con agua (20mL) y salmuera (10mL), se secaron (Na_2SO_4) y se evaporaron. Cromatografía en columna del residuo (ISOLUTE SI, 50g/150 ml), eluyendo con EtOAc y heptano (50:50), luego EtOAc y, a continuación, MeOH y EtOAc (1:99, 2:98 y 5:95), produjo el compuesto del título (0.461g, 57.5%) como un sólido blanco. ^1H NMR (400 MHz, CDCl3): 1.42 (s, 9H), 2.53 (d, 2H), 2.85-2.96 (m, 1H), 3.60 (dd, 2H), 4.09 (t, 2H), 5.78 (s, br, 2H); ^{13}C NMR (100 MHz, CDCl3): 25.4, 28.3, 39.7, 54.3 (br), 79.4, 156.3, 173.2.

terc-Butil 3-(2-aminoetil)azetidin-1-carboxilato

terc-Butil 3-(2-amino-2-oxoetil)azetidin-1-carboxilato (70mg, 0.327mmol) se disolvió en THF (2mL) y se enfrió en un baño helado. Se agregó gota a gota un complejo de borano - sulfuro de dimetilo (0.41mL, 2M en THF), tras lo cual la mezcla se hizo refluir durante 6 horas. La mezcla de reacción se dejó alcanzar la temperatura ambiente, y se agregó una mezcla de DIPEA:MeOH (0.6mL, 1:2) y yodo (166mg, 0.654mmol). La mezcla se agitó a temperatura de la sala de un día para otro y luego se evaporó a sequedad. Agua (5mL) y EtOAc (5mL) se agregaron al residuo, y las dos fases se separaron. Se agregó $NaHCO_3$ acuoso saturado (1mL) en la fase acuosa, y se extrajo con EtOAc (5mLx4). NaOH (1M, aprox. 1mL) se agregó en la fase acuosa y se extrajo con EtOAc (5mLx2). Los extractos se combinaron, se secaron (Na_2SO_4) y se evaporaron, y el residuo se purificó usando una columna de intercambio iónico (ISOLUTE PRS, 2g/15mL),

eluyendo con MeOH y DCM (10:90), luego MeOH y, a continuación, MeOH (saturado con NH_3) para producir el compuesto del título (35mg, 53.5%). ^{1}H NMR (400 MHz, CDCl3): 1.41 (s, 9H), 1.71 (dt, 2H), 2.49-2.60 (m, 1H), 2.64 (t, 2H), 3.54 (dd, 2H), 3.99 (t, 2H); ^{13}C NMR (100 MHz, CDCl3): 26.6, 28.3, 38.3, 39.8, 54.3 (br), 79.1, 156.3.

terc-Butil [2-(4-bromofenil)etil]carbamato

[2-(4-Bromofenil)etil]amina (2.20g, 11.00mmol) se disolvió en THF seco (77mL) y se agregó TEA (1.11g, 11.00mmol). La mezcla se enfrió en un baño helado. Se agregó di-_terc_-butil dicarbonato (2.40g, 11.00mmol). La mezcla se agitó durante 1 hora a 0°C y se dejó a temperatura de la sala de un día para otro. El disolvente se evaporó, y cromatografía en columna del producto crudo (ISOLUTE SI (20g), Heptano/EtOAc (90:10)) produjo el compuesto del título (3.18g, 96.3%). ^{1}H NMR (500MHz, CD_3OD): δ 1.42 (s, 9H), 2.73 (t, 2H), 3.25 (t, 2H), 7.14 (d, 2H), 7.43 (d, 2H).

terc-Butil [2-(4-cianofenil)etil]carbamato

terc-Butil [2-(4-bromofenil)etil]carbamato (0.52g, 1.73mmol) se disolvió en DMF seco (17mL) bajo una atmósfera de nitrógeno. Se agregaron cianuro de zinc (0.41g, 3.46mmol) y tetrakis(trifenilfosfina)paladio (0.16g, 0.14mmol). La mezcla de reacción se calentó en un reactor microondas a 150°C durante 20minutos. Se repitió el procedimiento dos veces más con una cantidad igual de material de partida, y las tres mezclas resultantes se combinaron. La mezcla se diluyó con EtOAc, se lavó con $NaHCO_3$ acuoso saturado y agua, se secó con Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó usando un sistema HPFC Biotage Horizon (columna 40+M, ciclo isocrático DCM/MeOH (99.5:0.5, 960mL), ciclo de gradiente DCM/MeOH (99.5:0.5-92:8, 240mL), ciclo isocrático DCM/MeOH (92:8, 720mL)), lo cual proporcionó el compuesto del título (1.14g, 88.9%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.88 (t, 2H), 3.40 (q, 2H), 4.58 (bs, 1H), 7.32 (d, 2H), 7.61 (d, 2H); Espectro de Masa: $M+H^+$ 247.

4-(2-Aminoetil)benzonitrilo

terc-Butil [2-(4-cianofenil)etil]carbamato (1.14g, 4.62mmol) se disolvió en DCM (6mL) y se agregó TFA (5mL). La mezcla se concentró y se disolvió

en EtOAc, y la fase orgánica se lavó con K_2CO_3 acuoso saturado Las capas orgánicas se secaron con Na_2SO_4, se filtraron y se evaporaron, lo cual proporcionó el compuesto del título (0.50g, 74.3%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.21 (bs, 2H), 2.81 (t, 2H), 2.99 (t, 2H), 7.31 (d, 2H), 7.58 (d, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 40.38, 43.31, 110.33, 119.23, 129.86, 132.48, 145.93.

***terc*-Butil 3-hidroxipirrolidin-1-carboxilato**

terc-Butil 3-oxopirrolidin-1-carboxilato (3.00g, 16.20mmol) se disolvió en MeOH seco (60mL) y se enfrió en un baño de agua helada. Se agregó cuidadosamente borohidruro de sodio (0.61g, 16.20mmol) y la mezcla de reacción se agitó a 0°C durante 15minutos. La mezcla de reacción se diluyó con agua, y el pH se ajustó a ~9 con HCl (1% de solución acuosa). La capa acuosa se extrajo con EtOAc, y las capas orgánicas se combinaron, se secaron con $MgSO_4$, se filtraron y se evaporaron para producir el compuesto del título (3.00g, 98.9%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.85-1.96 (m, 2H), 3.26-3.33 (m, 2H), 3.38-3.47 (m, 3H), 4.38-4.40 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.72, 33.95, 43.99, 54.38, 70.60, 79.57, 155.07.

***terc*-Butil 3-[(metilsulfonil)oxi]pirrolidin-1-carboxilato**

terc-Butil 3-hidroxipirrolidin-1-carboxilato (3.00g, 16.02mmol) se disolvió en DCM seco (50mL) y se enfrió en un baño de agua helada. Se agregó cloruro de metanosulfonilo (2.38g, 20.83mmol), seguido por TEA (2.43g, 24.03 mmol) y la mezcla de reacción se agitó a 0°C durante 3.5 horas. La mezcla de reacción se lavó con agua (250mL) y se secó con $MgSO_4$, se filtró y se evaporó. El producto crudo se purificó usando un sistema HPFC Biotage Horizon (columna 40+M, ciclo isocrático heptano/EtOAc (50:50)) proporcionando el compuesto del título (2.70g, 63.5%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.07 (bs, 1H), 2.18 (bs, 1H), 2.97 (s, 3H), 3.35-3.61 (m, 4H), 5.16-5.18 (m, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.59, 31.84, 32.76, 38.80, 43.61, 52.16, 80.12, 154.30.

***terc*-Butil 3-(acetiltio)pirrolidin-1-carboxilato**

Carbamato de potasio (4.42g, 31.96mmol) se suspendió en MeOH seco (20mL) y se agregó ácido tioacético (2.28g, 29.96mmol). La mezcla se agitó vigorosamente durante 10 minutos, se concentró y se diluyó en DMF seco (30mL). Se agregó *terc*-butil 3-[(metilsulfonil)oxi]pirrolidin-1-carboxilato (2.65g, 9.99mmol) disuelto en DMF seco (20mL), y la mezcla de reacción se calentó a 60°C durante 3.5 horas. La mezcla de reacción se diluyó con agua (350mL) y se extrajo con EtOAc (2x150mL). Las fases orgánicas se secaron con $MgSO_4$, se filtraron y se evaporaron. El producto crudo se purificó usando un sistema HPFC Biotage Horizon (columna 25+M, ciclo isocrático heptano/EtOAc (60:40)) proporcionando el compuesto del título (0.592g, 24.2%) (el producto es una mezcla de cis y trans isómeros).^{1}H NMR (500MHz, $CDCl_3$): δ 1.41 (d, 18H), 1.66 (d, 1H), 1.74-1.86 (m, 2H), 2.20-2.26 (m, 2H), 2.29 (s, 3H), 3.10-3.26 (m, 2H), 3.30-3.43 (m, 4H), 3.46-3.54 (m, 1H), 3.66-3.74 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.68, 30.82, 31.25, 32.34, 36.16, 41.09, 44.88, 51.60, 55.37, 79.67, 154.43; Espectro de Masa: $M+H^+$ 241.

***terc*-Butil 3-mercaptopirrolidin-1-carboxilato**

terc-Butil 3-(acetiltio)pirrolidin-1-carboxilato (200mg, 0.81mmol) se disolvió en MeOH (10mL), y se agregó metanotiolato de sodio (57mg, 0.81mmol). La mezcla de reacción se agitó a temperatura de la sala durante 30 minutos. Se agregó HCl (solución 1M), y la capa acuosa se extrajo con DCM. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4), se filtró y se evaporó, proporcionando el compuesto del título (0.163g, 98.4%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.68 (d, 1H), 1.75-1.84 (m, 1H), 2.22-2.28 (m, 1H), 3.13-3.23 (m, 1H), 3.30-3.40 (m, 2H), 3.47-3.57 (m, 1H), 3.67-3.74 (m, 1H).

[3-(Piridin-2-iloxi)propil]amina

3-Aminopropan-1-ol (0.28ml, 3.64mmol) se agregó a una mezcla de NaH (60% dispersión en aceite mineral) (16mg, 4.11mmol) en THF seco (8ml) a temperatura de la sala. La mezcla resultante se calentó a reflujo durante 35 minutos y se enfrió a temperatura ambiente antes de agregar 2-

bromopiridina (0.50g, 3.16mmol). La mezcla se hizo entonces refluir durante 2 horas 20 minutos y se agitó a temperatura de la sala durante otras 17 horas, antes de agregar más NaH (127mg, 3.16mmol), y la mezcla se calentó a reflujo durante 3 horas. La mezcla se evaporó a sequedad, se agregó agua, y la mezcla se acidificó a pH 5 con 1N HCl y se lavó con DCM. Seguidamente la fase acuosa se basificó a pH 4 y se extrajo de nuevo con DCM. Los extractos orgánicos se combinaron y se evaporaron para producir el compuesto del título (0.206g, 43%) como un aceite. ^{1}H NMR (500MHz $CDCl_3$): 8.17-8.12 (m, 1H), 7.58-7.53 (m, 1H), 6.67-6.63 (m, 1H), 6.72 (d, 1H), 4.39 (t, 2H), 2.88 (t, 2H), 1.93 (quintet, 2H). ^{13}C NMR (125MHz CDCl3): 164.1, 147.1, 138.7, 116.8, 111.3, 63.8, 39.5, 33.3.

***terc*-Butil [1-(5-metilpiridin-2-il)piperidin-4-il)carbamato**

Una solución de 2-bromo-5-rnetilpiridina (1.00g, 5.8mmol), *terc*-butil piperidin-4-ilcarbamato (1.28g, 6.39mmol) y TEA (1.21ml, 8.72mmol) en DMSO (5ml) se calentó a 110°C. Luego de 17 horas, la mezcla de reacción se calentó a 130°C durante 4 horas, antes de agregar más TEA (0.40ml, 2.91mmol). Luego de 2.5 horas, se agregó DBU (1.73ml, 11.63mmol), y la mezcla de reacción se calentó a 110°C durante 17 horas. La mezcla de reacción se dejó entonces enfriar a temperatura de la sala, y se agregó EtOAc. La mezcla de reacción se lavó con salmuera y se evaporó a sequedad. El residuo se purificó usando el Biotage SP1 eluyendo con 25% EtOAc en éter de petróleo 40-60°C para producir el compuesto del título (0.233g, 14%) como un sólido. ^{1}H NMR(500MHz, $CDCl_3$): 8.02 (d, 1H), 7.31 (dd, 1H), 6.62 (d, 1H), 4.48 (bs, 1H), 4.16-4.10 (m, 2H), 3.68 (bs, 1H), 2.95 (dt, 2H), 2.20 (s, 3H), 2.08-2.00 (m, 2H), 1.48-1.40 (m, 9H). ^{13}C NMR($CDCl_3$): 158.1, 155.4, 147.9, 138.6, 122.3, 107.5, 79.5, 48.4, 45.1, 32.3, 28.7, 17.5. Espectro de Masa: M+H 292.

Clorhidrato de 1-(5-metilpiridin-2-il)piperidin-4-amina

Una solución de *terc*-butil [1-(5-metilpiridin-2-il)piperidin-4-il)carbamato (0.23g, 0.79mmol) en HCl en dioxano (4M, 2ml), THF (1ml) y MeOH (1ml) se agitó a temperatura de la sala. Luego de 17 horas, la mezcla de

reacción se filtró, y el residuo se lavó con EtOAc y se secó para producir el compuesto del título (181mg, 86.8%) como un sólido. ^{1}H NMR(500MHz, D_2O): 7.80 (d, 1H), 7.60 (s, 1H), 7.15 (d, 1H), 4.10-4.03 (m, 2), 3.53-3.44 (m, 1H), 3.21 (t, 2H), 2.16-2.10 (m, 5H), 1.65 (dq, 2H); ^{13}C NMR(D_2O): 150.8, 146.8, 133.9, 123.9, 112.9, 47.7, 44.7, 28.8; Espectro de Masa: M+H 192

***terc*-Butil [1-(6-cloropiridazin-3-il)piperidin-4-il]carbamato**

terc-Butil piperidin-4-ilcarbamato (2g, 10 mmol), 3,6-dicloropiridazina (1.79g, 12 mmol) y TEA (2.1 ml, 15 mmol) se disolvieron en DMF seco (30 ml), y la mezcla de reacción se calentó en un reactor microondas a 150°C durante 20 minutos. La mezcla de reacción se diluyó con agua (300 ml) y se extrajo con EtOAc (300 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 98:2 de DCM:MeOH para producir el compuesto del título (2.11g, 68%) como un sólido. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, 1H), 6.91 (d, 1H), 4.48 (bs, 1H), 4.29-4.20 (m, 2H), 3.73 (bs, 1H), 3.14-3.04 (m, 2H), 2.10-2.02 (m, 2H), 1.49-1.38 (m, 2H), 1.45 (s, 9H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 158.9, 155.2, 146.7, 128.9, 115.5, 79.6, 47.9, 44.4, 31.9, 28.5.

1-(6-Cloropiridazin-3-il)piperidin-4-amina

terc-Butil éster de ácido [1-(6-cloro-piridazin-3-il)-piperidin-4-il]-carbámico (0.59g 1.89 mmol) se disolvió en THF:MeOH 2:1 (45 ml), y se agregó HCl en 1,4-dioxano (4M, 3.8 ml, 7.56 mmol). La reacción se agitó a temperatura de la sala durante 3 horas y luego a 60°C durante 2 horas. El disolvente se evaporó para proporcionar el compuesto del título (0.49g, 100%) como la sal clorhidrato. ^{1}H-NMR (CD_3OD, 500 MHz): δ 8.10 (d, 1H), 7.92 (d, 1H), 4.41-4.35 (m, 2H), 3.67-3.57 (m, 1H), 3.55- 3.46 (m, 2H), 2.32-2.24 (m, 2H), 1.96-1.83 (m, 2H).

***terc*-Butil [1-(6-metoxipiridazin-3-il)piperidin-4-il]carbamato**

terc-Butil [1-(6-cloropiridazin-3-il)piperidin-4-il]carbamato (0.50g, 1.60 mmol) se disolvió en MeOH seco (15 ml), y se agregó metal sodio (0.073g, 3.20 mmol) disuelto en MeOH (5 ml). La mezcla de reacción se calentó en

un reactor microondas a 120°C durante 4 horas. La mezcla se diluyó con agua (500 ml) y se extrajo con EtOAc (200 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar el compuesto del título (0.37g, 75%).

1-(6-Metoxipiridazin-3-il)piperidin-4-amina

terc-Butil éster de ácido [1-(6-metoxi-piridazin-3-il)-piperidin-4-il]-carbámico (0.37, 1.2 mmol) se disolvió en THF:MeOH 9:1 (15 ml), y se agregó HCl en 1,4-dioxano (4M, 1.2 ml, 4.8 mmol). La mezcla de reacción se calentó a 60°C durante 3 horas. El disolvente se evaporó para proporcionar el compuesto del título (0.35g, 100%) como la sal diclorhídrica. ^{1}H-NMR (CD_3OD, 500 MHz): δ 8.04 (d, 1H), 7.57 (d, 1H), 4.34-4.26 (m, 2H), 4.00 (s, 3H), 3.62-3.55 (m, 1H), 3.50-3.40 (m, 2H), 2.30-2.23 (m, 2H), 1.90-1.79 (m, 2H); ^{13}C-NMR (CD_3OD, 125 MHz): δ 159.7, 152.1, 129.8, 127.0, 62.1, 55.9, 46.2, 45,9, 45.7, 30.9, 30.3, 30.1.

***terc*-Butil (1-piridazin-3-ilpiperidin-4-il)carbamato**

terc-Butil [1-(6-cloropiridazin-3-il)piperidin-4-il]carbamato (0.5g, 1.60 mmol) se disolvió en MeOH (20 ml) y se enfrió a 0°C con un baño helado. Se agregó 10% Pd/C (60 mg) cuidadosamente. Se agregó formiato de amonio (0.30g, 4.80 mmol), y la mezcla de reacción se calentó a 40°C. Se agregó formiato de amonio (0.604g, 9.59 mmol) en porciones durante la reacción; luego de 33 horas a 40°C, la mezcla de reacción se filtró a través de celita y la celita se lavó con MeOH (20 ml). La mezcla de reacción se evaporó y el residuo se diluyó con EtOAc (100mL) y se lavó con agua (200 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 98:2 de DCM:MeOH para producir el compuesto del título como un sólido (0.25g, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.52-8.47 (m, 1H), 7.17-7.11 (m, 1H), 6.91-6.84 (m, 1H), 4.67-4.57 (m, 1H), 4.30-4.21 (m, 2H), 3.75-3.62 (m, 1H), 3.09-2.99 (m, 2H), 2.05-1.96 (m, 2H), 1.46-1.35 (m, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 155.4, 143.3, 127.5, 112.7, 79.6, 48.2, 44.3, 32.1, 28.6.

1-Piridazin-3-ilpiperidin-4-amina

terc-Butil (1-piridazin-3-ilpiperidin-4-il)carbamato (0.22g, 0.92 mmol) se disolvió en THF:MeOH 70:30 (15 ml), y se agregó HCl en 1,4-dioxano (4M, 1.84 ml, 7.36 mmol) y la mezcla se hizo refluir durante 1.5 horas. La mezcla de reacción se evaporó para proporcionar el compuesto del título (0.250g, 100%) como la sal diclorhídrica. (0.250g, 100%). ^{1}H NMR (CD_3OD, 500 MHz): δ 8.72-8.67 (m, 1H), 8.14-8.07 (m, 1H), 8.03-7.97 (m, 1H), 4.55-4.45 (m, 2H), 3.62- 3.51 (m, 1H), 3.38-3.27 (m, 2H), 2.27-2.18 (m, 2H), 1.82-1.70 (m, 2H)

***terc*-Butil{1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il} carbamato**

Una mezcla de 2,3-dicloro-5-(trifluorometil)piridina (2.0g, 9.26mmol), *terc*-butil piperidin-4-ilcarbamato(2.2g, 11.11mmol) y carbamato de potasio anhidro (3.8g, 27.78mmol) en DMF (15ml) se calentó en un reactor microondas a 150°C durante 10 minutos. La mezcla se concentró, se agregaron agua y EtOAc al residuo y la fase acuosa se extrajo con EtOAc. Las fases orgánicas se secaron sobre Na_2SO_4 y se concentraron. El producto crudo se purificó por cromatografía rápida en columna (hexano/EtOAc 90:10) para proporcionar el compuesto del título (2.5g, 70%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.47 s, 9H), 1.53-1.60 (m, 2H), 2.07-2.09 (m, 2H), 3.01-3.06 (m, 2H), 3.72 (br.s., 1H), 3.97- 4.00 (m, 2H), 4.54 (br.s., 1H), 7.75 (s, 1H), 8.38 (s, 1H); Espectro de Masa: $M+H^+$ 380.

1-[3-Cloro-5-(trifluorometil)-piridin-2-il]piperidin-4-amina

terc-Butil{1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il} carbamato (2.5g, 6.4mmol) se agitó en una mezcla de THF (25ml), MeOH (5ml) y HCl en dioxano (4M, 6.5ml) de un día para otro a temperatura de la sala. Se agregó HCl en dioxano (4M, 4ml) y, luego de 4 horas, se agregó una tercera porción de HCl en dioxano (4M, 4ml). Se continuó la agitación durante 48 horas a temperatura de la sala. El disolvente se evaporó, y el residuo se disolvió en EtOAc. La mezcla resultante se lavó con Na_2CO_3 acuoso saturado, agua, y se secó sobre Na_2SO_4. La concentración de la fase orgánica produjo el compuesto del título (2.3g, 128%), el cual contenía

algunas impurezas. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.50-1.54 (m, 2H), 1.88-1.94 (m, 2H), 2.93-3.00 (m, 3H), 4.01-4.04 (m, 2H), 7.74 (s, 1H), 8.38 (s, 1H); Espectro de Masa: $M+H^+$ 280.

2-(Benciloxi)fenil metanosulfonato

2-(Benciloxi)fenol (3.00g, 14.98mmol) se disolvió en DCM seco (70mL) bajo una atmósfera de nitrógeno y se enfrió en un baño de agua helada. Se agregó cloruro de metanosulfonilo (2.06g, 17.98mmol) durante la agitación, seguida por TEA (2.27g, 22.47mmol). La mezcla de reacción se agitó a temperatura de la sala durante 2 horas, y luego se lavó con $NaHCO_3$ acuoso saturado, se secó ($MgSO_4$), se filtró y se evaporó, proporcionando el compuesto del título (4.04g, 96.9%). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.09 (s, 3H), 5.15 (s, 2H), 7.02 (dt, 1H), 7.09 (dd, 1H), 7.27 (dt, 1H), 7.34-7.48 (m, 6H); ^{13}C NMR (125MHz, $CDCl_3$): δ 38.72, 71.37, 114.67, 121.79, 125.06, 127.95, 128.50, 128.68, 129.00, 136.20, 138.96, 150.91.

2-Hidroxifenil metanosulfonato

2-(Benciloxi)fenil metanosulfonato (4.00g, 14.37mmol) se disolvió en DCM seco (50mL) bajo una atmósfera de nitrógeno. Se agregó dietil eterato de trifluoruro de boro (8.16g, 57.49mmol), seguido por sulfuro de dimetilo(3.57g, 57.49mmol), y la mezcla de reacción se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se vertió sobre hielo, y la capa acuosa se extrajo con DCM. Las capas orgánicas se combinaron, se lavaron con agua, se secaron (Na_2SO_4), se filtraron y se evaporaron para producir el compuesto del título (2.49g, 92%). ^{1}H NMR (500MHz, $CDCl_3$): 63.26 (s, 3H), 6.16 (s, 1H), 6.96 (dt, 1H), 7.09 (dd, 1H), 7.22-7.28 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 37.74, 119.01, 121.65, 123.71, 129.09, 136.99, 148.43; Espectro de Masa: $M-H^+$ 187.

***terc*-Butil [1-(6-cloropiridin-3-il)piperidin-4-il]carbamato**

Paso 1: Una solución de 2-cloro-5-fluoropiridina (1.77g, 13.47mmol), *terc*-butil piperidin-4-ilcarbamato (3.10g, 15.49mmol) y TEA (2.05mL, 14.81mmol) en DMSO (7mL) se calentó a 100°C durante 17 horas, 120°C durante 4 horas y 140°C durante 20 horas.

Paso 2: Una solución de 2-cloro-5-fluoropiridina (1.77g, 13.47mmol), *terc*-butil piperidin-4-ilcarbamato (2.83g, 14.14mmol) y TEA (2.05ml, 14.81mmol) en DMSO (7ml) se calentó a 140°C durante 17 horas. Se agregó *terc*-butil piperidin-4-ilcarbamato (0.269g, 1.35mmol), y la mezcla de reacción se calentó a 140°C durante 17 horas y luego a 155°C durante 8 horas, y la mezcla de reacción se enfrió a temperatura de la sala.

Se agregó EtOAc a las mezclas de reacción combinadas del Paso 1 y Paso 2, y la fase orgánica se lavó con agua y salmuera antes de evaporar a sequedad. El residuo se purificó usando el sistema HPFC Biotage Horizon eluyendo con 10-65% EtOAc en éter de petróleo (40-60°C) para producir el compuesto del título (1.21g, 29%) como un sólido. ^{1}H NMR(500MHz, CDCl3): 8.02 (d, 1H), 7.21-7.12 (m, 2H), 4.50 (bs, 1H), 3.64 (bs, 1H), 3.64-3.54 (m, 2H), 2.89 (dt, 2H), 2.12-2.04 (m, 2H), 1.60-1.48 (m, 2H), 1.47 (s, 9H); ^{13}C NMR($CDCl_3$): 155.3, 146.3, 141.3, 138.1, 126.4, 124.1, 79.8, 48.2, 47.6, 32.2, 28.6; Espectro de Masa: M+H 312

Diclorhidrato de 1-(6-cloropiridin-3-il)piperidin-4-amina

Una solución de *terc*-butil [1-(6-cloropiridin-3-il)-piperidin-4-il)carbamato (1.211g, 3.88mmol) en HCl en dioxano (4M, 5mL), THF (5mL) y MeOH (4mL) se agitó a temperatura de la sala durante 20 horas. La mezcla de reacción se filtró, el residuo se lavó con EtOAc y se secó para producir el compuesto del título (1.02g, 92%) como un sólido; ^{1}H NMR (500MHz, CD_3OD): 8.36 (d, 1H), 7.97 (dd, 1H), 7.68 (d, 1H), 4.05-3.96 (m, 2H), 3.51-3.41 (m, 1H), 3.18 (dt, 2H), 2.24-2.17 (m, 2H), 1.85 (dq, 2H); ^{13}C NMR(CD_3OD): 145.8, 136.7, 133.3, 130.7, 126.5, 47.1, 28.9; Espectro de Masa: M+H 212.

Ácido carbámico, [2-[[[3-(difluorometoxi)fenil]metil]amino]-2-oxoetil]-1,1-dimetiletil éster

N-(*terc*-Butoxicarbonil)glicina (1.01g, 5.78mmol) se disolvió en DMF seco (12mL), y se agregó DIPEA (2.24g, 17.33mmol), seguido por HOAt (0.87g, 6.35mmol) y EDC (1.44g, 7.51mmol). La mezcla de reacción se agitó a temperatura de la sala durante 30 minutos, seguidos por la adición de [3-(difluorometoxi)bencil]amina (1.00g, 5.78mmol). La mezcla se agitó a

temperatura de la sala de un día para otro. La mezcla de reacción se diluyó con EtOAc y se lavó con agua. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó en un sistema HPFC Biotage Horizon usando DCM y MeOH como eluyente, lo cual proporcionó el compuesto del título (1.59g, 83.3%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.84 (d, 2H), 4.47 (d, 2H), 5.27 (bs, 1H), 6.52 (t, J_{C-F}=73.6Hz, 1H), 6.75 (bs, 1H), 7.02-7.04 (m, 2H), 7.13 (d, 1H), 7.30-15 7.34 (m, 1H); Espectro de Masa: M-H$^+$ 329.

N^1-[3-(Difluorometoxi)bencil]glicinamida

Ácido carbámico, [2-[[[3-(difluorometoxi)fenil]metil]amino]-2-oxoetil]-1,1- dimetiletil éster (1.58g, 12.62mmol) se disolvió en DCM (6mL), y se agregó TFA (5mL). La mezcla de reacción se agitó a temperatura de la sala durante 1hora. La mezcla se concentró se diluyó con EtOAc y se lavó con K_2CO_3 acuoso saturado. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó, lo cual proporcionó el compuesto del título (1.07g, 97.2%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.49 (bs, 2H), 3.42 (s, 2H), 4.49 (d, 2H), 6.52 (t, J_{C-F}=73.8Hz, 1H), 7.02- 7.06 (m, 2H), 7.15 (d, 1H), 7.33 (t, 1H), 7.72 (bs, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 42.70, 44.95, 116.13 (t, J_{C-F}=259.4Hz), 118.52, 118.95, 124.84, 130.29, 141.07, 151.70, 173.01; Espectro de Masa: M+H$^+$ 231.

***terc*-Butil (1-piridin-2-ilpiperidin-4-il)carbamato**

Una solución de 2-cloropiridina (0.83ml, 8.81mmol), *terc*-butil piperidin-4-ilcarbamato (1.85g, 9.24mmol) y TEA (0.98mL, 9.69mmol) en DMSO (5mL) se calentó a 120°C durante 4 horas 45 minutos y, a continuación, se calentó a 140°C durante 2 días. Se agregó EtOAc, y la fase orgánica se lavó con agua, luego salmuera antes de evaporar a sequedad. El residuo se purificó en un sistema Biotage Horizion HPFC eluyendo con 20% EtOAc en éter de petróleo (40-60°C) para producir el compuesto del título (0.65mg, 27%). ^{1}H NMR(500MHZ, $CDCl_3$): 8.19 (s, 1H), 7.48 (dd, 1H), 6.67 (d, 1H), 6.61 (t, 1H), 4.49 (bs, 1H), 4.21 (d, 2H), 3.70 (bs, 1H), 2.99 (t, 2H), 2.05 (d, 2H), 1.59-1.38 (m, HH). 13C NMR($CDCl_3$): 159.5, 155.4,

148.2, 137.7, 113.3, 107.5, 79.6, 48.4, 44.6, 32.3, 28.7; Espectro de Masa: M+H 278.

Diclorhidrato de 1-piridin-2-ilpiperidin-4-amina

Una solución de *terc*-butil (1-piridin-2-ilpiperidin-4-il)carbamato (0.64g, 2.31mmol) en HCl en dioxano (4M, 3.5ml), THF (2.5ml) y MeOH (2ml) se agitó a temperatura de la sala durante 17 horas. La mezcla de reacción se filtró, el residuo se lavó con EtOAc y se secó para producir el compuesto del título (0.49mg, 85%) como un sólido. ^{1}H NMR(500MHz, D_2O): 7.91 (dd, 1H), 7.78 (d, 1H), 7.22 (d, 1H), 6.88 (t, 1H), 4.12 (d, 2H), 3.56-3.48 (m, 1H), 3.26 (t, 2H), 2.15 (d, 2H), 1.67 (dq, 2H); ^{13}C NMR(D_2O): 152.1, 144.7, 135.9, 113.3, 47.6, 44.7, 28.8; Espectro de Masa: M+H 178

***terc*-Butil [1-(5-fluoropiridin-2-il)piperidin-4-il]carbamato**

Paso 1: Una solución de 2-cloro-5-fluoropiridina (1.77 g, 13.47mmol), *terc*-butil piperidin-4-ilcarbamato (3.10g, 15.49mmol) y TEA (2.05mL, 14.81mmol) en DMSO (7mL) se calentó a 100°C durante 17 horas, 120°C durante 4 horas y 140°C durante 20 horas.

Paso 2: Una solución de 2-cloro-5-fluoropiridina (1.77g, 13.47mmol), *terc*-butil piperidin-4-ilcarbamato (2.83g, 14.14mmol) y TEA (2.05mL, 14.81mmol) en DMSO (7mL) se calentó a 140°C durante 17 horas. Se agregó *terc*-butil piperidin-4-ilcarbamato (0.269g, 1.35mmol) y la mezcla de reacción se calentó a 140°C durante 17 horas y luego a 155°C durante 8 horas antes de enfriar a temperatura de la sala.

EtOAc se agregó a las mezclas de reacción combinadas de Paso 1 y Paso 2, y la fase orgánica se lavó con agua y salmuera antes de evaporar a sequedad. El residuo se purificó usando el sistema HPFC Biotage Horizon, eluyendo con 10-65% EtOAc en éter de petróleo (40-60°C) para producir el compuesto del título (0.368g, 9%) como un sólido. ^{1}H NMR(500MHz, $CDCl_3$): 8.05 (d, 1H), 7.27-7.20 (m, 1H), 6.64 (dd, 1H), 4.49 (bs, 1H), 4.16-4.04 (m, 2H), 3.68 (bs, 1H), 2.96 (dt, 2H), 2.10-2.00 (m, 2H), 1.56-1.40 (m, HH); ^{13}C NMR($CDCl_3$): 156.6, 155.4, 154.6, 152.6, 134.9, 134.8, 125.3, 125.1, 108.2, 108.1, 79.7, 48.2, 45.5, 32.3, 28.6; Espectro de Masa: M+H 296.

Diclorhidrato de 1-(5-fluoropiridin-2-il)piperidin-4-amina

Una solución de *terc*-butil (1-(5-fluoropiridin-2-il)piperidin-4-il)carbamato (0.36g, 1.22mmol) en HCl en dioxano (4M, 2mL), THF (2mL) y MeOH (2mL) se agitó a temperatura de la sala. Luego de 4 horas, la mezcla de reacción se filtró, el residuo se lavó con EtOAc y se secó para producir el compuesto del título (0.31g, 96%) como un sólido. ^{1}H NMR (500MHz, CD_3OD): 8.10-8.02 (m, 2H), 7.52 (dd, 1H), 4.34-4.26 (m, 2H), 3.61-3.50 (m, 1H), 3.38 (dt, 2H), 2.28-2.21 (m, 2H), 1.80 (dq, 2H); ^{13}C NMR(CD_3OD): 153.2, 151.2, 151.0, 134.5, 134.3, 123.9, 123.6, 115.0, 114.9, 45.3, 29.1; Espectro de Masa: M+H 196.

***terc*-Butil [1-(5-cloropiridin-2-il)piperidin-4-il]carbamato**

Una solución de 2,5-dicoloropiridina (1.00g, 6.78mmol), *terc*-butil piperidin-4-ilcarbamato (1.42g, 7.06mmol) y TEA (1.03mL, 7.43mmol) en DMSO (5mL) se calentó a 120°C durante 21 horas y, en seguida, a 140°C durante 41 horas. Se agregó EtOAc, y la fase orgánica se lavó con agua, salmuera, y se evaporó a sequedad. El residuo se purificó usando el sistema Horizon HPFC, eluyendo con 0-20% EtOAc en DCM para producir el compuesto del título (1.16g, 55%) como un sólido. ^{1}H NMR (500MHz, $CDCl_3$): 8.10 (d, 1H), 7.41 (dd, 1H), 6.61 (d, 1H), 4.18 (bs, 1H), 4.20-4.12 (m, 2H), 3.70 (m, 2H), 2.99 (dt, 2H), 2.08-1.98 (m, 2H), 1.58-1.38 (m, 11H); ^{13}C NMR($CDCl_3$): 157.8, 155.4, 146.5, 137.4, 120.1, 108.1, 79.7, 48.3, 44.8, 32.2, 28.6; Espectro de Masa: M+H 256.

Diclorhidrato de 1-(5-cloropiridin-2-il)piperidin-4-amina

Una solución de *terc*-butil (1-(5-cloropiridin-2-il)piperidin-4-il)carbamato (1.15g, 3.70mmol) en HCl en dioxano (4M, 5mL) y THF (5mL) se agitó a temperatura de la sala durante 6.5 horas. Se agregó 4M HCl en dioxano (2mL), y la mezcla de reacción se agitó durante otras 20 horas. La mezcla de reacción se filtró, el residuo se lavó con EtOAc y se secó para producir el compuesto del título (1.06g, 100%) como un sólido. ^{1}H NMR(500MHz, CD_3OD): 8.10 (s, 1H), 8.06 (d, 1H), 7.52 (d, 1H), 4.36 (d, 2H), 3.62-3.54 (m, 1H), 3.42 (dt, 2H), 2.18 (d, 2H), 1.82 (dq, 2H); ^{13}C NMR(CD_3OD): 151.4, 144.4, 134.6, 120.0, 114.7, 45.2, 29.1; Espectro de Masa: M+H 212.

***terc*-Butil {1-[4-(trifluorometil)piridin-2-il]piperidin-4-il}carbamato**

Una solución de 2-bromo-4-trifluorometilpiridina (1.00g, 4.42mmol), *terc*-butil piperidin-4-ilcarbamato (0.93g, 4.65mmol) y TEA (0.67mL, 4.86mmol) en DMSO (5mL) se calentó a 120°C durante 17 horas. La mezcla de reacción se evaporó a sequedad, se agregó Et_2O, y la fase orgánica se lavó con agua, salmuera y se evaporó a sequedad. El residuo se purificó usando el sistema Biotage Horizon HRFC, eluyendo con 22% EtOAc en éter de petróleo (40-60°C) para producir el compuesto del título (1.08g, 71%) como un sólido. ^{1}H NMR (500MHz, $CDCl_3$): 8.30 (d, 1H), 6.82 (s, 1H), 6.77 (d, 1H), 4.49 (bs, 1H), 4.36-4.22 (m, 2H), 3.74 (bs, 1H), 3.06 (td, 2H), 2.10-2.04 (m, 2H), 1.56-1.38 (m, 11H); ^{13}C NMR($CDCl_3$): 159.4, 155.4, 149.5, 140.1, 139.9, 124.5, 122.4, 108.1, 102.7, 79.8, 48.3, 44.4, 32.3, 28.6; Espectro de Masa: M+H 346.

1-[4-(Trifluorometil)piridin-2-il]piperidin-4-amina

Una solución de *terc*-butil {1-[4-(trifluorometil)piridin-2-il)piperidin-4-il) carbamato (1.07g, 3.09mmol) en HCl en dioxano (4M, 5mL) y THF (5mL) se agitó a temperatura de la sala durante 6.5h oras. Se agregó HCl en dioxano (4M, 2mL), y la mezcla de reacción se agitó durante otras 20 horas. La mezcla de reacción se filtró, el residuo se lavó con EtOAc y se secó para producir el compuesto del título (0.99g, 100%) como un sólido. ^{1}H NMR(500MHz, CD_3OD): 8.19 (d, 1H), 7.82 (s, 1H), 7.22 (d, 1H), 4.64 (d, 2H), 3.66-3.56 (m, 1H), 3.52 (td, 2H), 3.29 (d, 2H), 1.87 (dq, 2H); ^{13}C NMR(CD_3OD): 152.6, 144.8, 144.5, 144.2, 143.9, 138.7, 125.3, 123.1, 120.9, 118.7, 111.2, 108.1, 45.3, 29.0; Espectro de Masa: M+H 246

***terc*-Butil [2-(3-bromofenil)etil]carbamato**

[2-(3-Bromofenil)etil]amina (2.22g, 11.09 mmol) se disolvió en THF seco (80mL), y se agregó TEA (1.12g, 11.09 mmol). La mezcla se enfrió en un baño helado. Se agregó di-*terc*-butil dicarbonato (2.42g, 11.09mmol). La mezcla de reacción se agitó durante 1 hora a 0°C y a temperatura de la sala durante 2 horas. El disolvente se evaporó, lo cual proporcionó el compuesto del título (3.44g, 103%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.79 (t, 2H), 3.37 (q, 2H), 4.58 (bs, 1H), 7.12-7.15 (m, 1H), 7.17-7.20 (m, 1H),

7.35-7.38 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.63, 36.11, 41.82, 79.61, 122.83, 127.71, 129.78, 130.35, 132.12, 141.64, 156.05; Espectro de Masa: M-Na^+ 323.

terc-Butil [2-(3-cianofenil)etil]carbamato

terc-Butil [2-(3-bromofenil)etil]carbamato (0.60g, 1.99mmol) se disolvió en DMF seco (18mL) bajo una atmósfera de nitrógeno. Se agregaron cianuro de zinc (0.47g, 3.99mmol) y tetrakis(trifenilfosfina)paladio (0.18g, 0.16mmol). La mezcla de reacción se calentó en un reactor microondas a 150°C durante 20minutos. Se repitió el procedimiento dos veces más con una cantidad igual de material de partida y las tres mezclas resultantes se combinaron y se diluyeron con EtOAc. La mezcla se lavó con $NaHCO_3$ acuoso saturado y agua, se secó con Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó usando un sistema HPFC Biotage Horizon, utilizando heptano y EtOAc como eluyente, lo cual proporcionó el compuesto del título (0.95g, 64.3%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.82 (t, 2H), 3.34 (q, 2H), 4.75 (bs, 1H), 7.37-7.50 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.57, 36.09, 41.63, 79.61, 112.69, 119.05, 129.56, 130.38, 132.57, 133.68, 140.86, 156.06.

3-(2-Aminoetil)benzonitrilo

terc-Butil [2-(3-cianofenil)etil]carbamato (0.949g, 3.853mmol) se disolvió en DCM (5mL) y TFA (4mL) y se agitaron a temperatura de la sala durante 2 horas. La mezcla se concentró y se re-disolvió en EtOAc. La mezcla se lavó con K_2CO_3 acuoso saturado, se secó sobre Na_2SO_4, se filtró y se evaporó, lo cual proporcionó el compuesto del título (0.40g, 71.7%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.18 (bs, 2H), 2.79 (t, 2H), 3.00 (t, 2H), 7.39-7.47 (m, 2H), 7.50-7.53 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 39.81, 43.42, 112.74, 119.17, 129.47, 130.24, 132.57, 133.66, 141.67.

4-(Benciloxi)fenil metanosulfonato

4-(Benciloxi)fenol (4.00g, 19.98mmol) se disolvió en DCM seco (80mL) bajo una atmósfera de nitrógeno y se enfrió en un baño de agua helada. Se agregó cloruro de metanosulfonilo (2.75g, 23.97mmol) durante la agitación, seguido por TEA (3.03g, 29.96mmol). La mezcla de reacción se agitó a

temperatura de la sala durante 2 horas y luego se lavó con $NaHCO_3$ acuoso saturado, se secó ($MgSO_4$), se filtró y se evaporó, proporcionando el compuesto del título (5.32g, 95.6%). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.13 (s, 3H), 5.08 (s, 2H), 7.01 (m, 2H), 7.23 (m, 2H), 7.35-7.45 (m, 5H).

4-Hidroxifenil metanosulfonato

4-(Benciloxi)fenil metanosulfonato (5.31g, 19.08mmol) se disolvió en DCM seco (70mL) bajo una atmósfera de nitrógeno. Se agregó dietil etearato de trifluoruro de boro (10.83g, 76.31mmol), seguido por sulfuro de dimetilo (4.74g, 76.31mmol), y la mezcla de reacción se agitó a temperatura de la sala durante 3 horas. La mezcla de reacción se vertió sobre hielo, y la capa acuosa se extrajo con DCM. Las capas orgánicas se combinaron, se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se evaporaron para producir el compuesto del título (2.96g, 82.5%). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.14 (s, 3H), 5.51 (s, 1H), 6.83 (d, 2H), 7.14 (d, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 37.35, 116.74, 123.49, 142.68, 155.06.

***terc*-Butil {1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-il} carbamato**

2,3-Dicloro-5-(trifluorometil)piridina (1.50g, 6.94mmol), *terc*-butil azetidin-3-ilcarbamato(1.67g, 9.72mmol) y K_2CO_3 (2.88g, 20.83mmol) se disolvieron en DMF seco (13mL) bajo una atmósfera de nitrógeno. La mezcla de reacción se calentó en un reactor microondas a 150°C durante 15 minutos. La mezcla de reacción se filtró y se diluyó con EtOAc, se lavó con agua, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto crudo se purificó por cromatografía en columna (ISOLUTE SI (20g), eluida con DCM, DCM/MeOH (99:1)), lo cual proporcionó el compuesto del título (0.85g, 34.8%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.48 (s, 9H), 4.10-4.14 (m, 2H), 4.57 (bs, 1H), 4.65 (t, 2H), 5.00 (bs, 1H), 7.61 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 28.56, 41.67, 60.34, 80.45, 115.51, 117.44 (q, J_{C-F}=33.2Hz), 123.83 (m, J_{C-F}=271.4Hz), 135.06, 143.75, 155.18, 157.35; Espectro de Masa: M-H$^+$ 350.

1-[3-Cloro-5-(trifluorometil)piridin-2-il]azetidin-3-amina

terc-Butil {1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-il} carbamato (0.85g, 2.42mmol) se disolvió en DCM (4mL) y TFA (3mL) y se agitó a temperatura de la sala durante 1 hora. La mezcla se concentró y se re-disolvió en EtOAc, se lavó con K_2CO_3 acuoso saturado. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó, lo cual proporcionó el compuesto del título (0.58g, 95.1%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.65 (bs, 2H), 3.91-3.98 (m, 3H), 4.57-4.61 (m, 2H), 7.58 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 43.68, 63.02, 115.38, 116.90 (q, J_{C-F}=33.2Hz), 123.91 (q, J_{C-F}=270.9Hz), 134.95, 143.76, 157.56; Espectro de Masa: M+H$^+$ 252.

Ácido carbámico, [2-oxo-2-[(fenilmetil)amino]etil]-, 1,1-dimetiletil éster

N-(*terc*-Butoxicarbonil)glicina (1.64g, 9.33mmol) se disolvió en DCM seco (20mL), y se agregó DIPEA (3.62g, 27.99mmol), seguido por HOAt (1.40g, 10.27mmol) y EDC (2.33g, 12.13mmol). La mezcla de reacción se agitó a temperatura de la sala durante 30 minutos, y se agregó bencilamina (1.00g, 9.33mmol). La mezcla se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se concentró y se diluyó con EtOAc, se lavó con $NaHCO_3$ acuoso saturado y agua. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó en un sistema HPFC Biotage Horizon usando DCM y MeOH como eluyente, lo cual proporcionó el compuesto del título (1.26g, 51%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.82 (d, 2H), 4.44 (d, 2H), 5.35 (bs, 1H), 6.73 (bs, 1H), 7.25-7.28 (m, 3H), 7.30-7.34 (m, 2H); Espectro de Masa: M+H$^+$ 265.

***N*^{1}-Bencilglicinamida**

Ácido carbámico, [2-oxo-2-[(fenilmetil)amino]etil]-,1,1-dimetiletil éster (1.25g, 12.62mmol) se disolvió en DCM (6mL), y se agregó TFA (5mL). La mezcla de reacción se agitó a temperatura de la sala durante 2 horas. La mezcla se concentró y se diluyó con EtOAc, y se lavó con K_2CO_3 acuoso saturado. La capa orgánica se secó con Na_2SO_4, se filtró y se evaporó, lo cual proporcionó el compuesto del título (0.73g, 94.5%). ^{1}H NMR

(500MHz, $CDCl_3$): δ 1.48 (bs, 2H), 3.38 (s, 2H), 4.46 (d, 2H), 7.26-7.35 (m, 5H), 7.64 (bs, 1H); ^{13}C NMR (125MHz, $CDCl_3$): 543.24, 45.00, 127.65, 127.99, 128.90, 138.66, 172.93; Espectro de Masa: $M+H^+$ 165.

***terc*-Butil (4-hidroxiciclohexil)carbamato**

4-Aminociclohexanol (5.00g, 43.41mmol) se disolvió en THF seco (250mL), y se agregó TEA (4.39g, 43.41mmol). La mezcla se enfrió en un baño helado. Se agregó di-*terc*-butil dicarbonato (9.47g, 43.41mmol), y la mezcla de reacción se agitó a 0°C durante 1 hora y se dejó de un día para otro a temperatura de la sala. El disolvente se evaporó, y la cromatografía en columna del producto crudo (ISOLUTE SI (20g) Heptano/EtOAc; 90:10-70:30) produjo el compuesto del título (6.13g, 65.6%) como una mezcla de cis y trans isómeros. ^1H NMR (500MHz, $CDCl_3$): δ 1.21-1.37 (m, 4H), 1.45 (d, 9H), 1.53 (s, 9H), 1.57-1.73 (m, 8H), 1.88-1.96 (m, 4H), 3.25-3.31 (m, 1H), 3.40 (bs, 1H), 3.48-3.54 (m, 1H), 3.80-3.84 (m, 1H).

4-[(*terc*-Butoxicarbonil)amino]ciclohexil metanosulfonato

terc-Butil (4-hidroxiciclohexil)carbamato (2.5g, 11.61 mmol) y TEA (3.23 ml, 23.22 mmol) se disolvió en DCM (50 ml) y se enfrió a 0°C con un baño helado. Se agregó gota a gota cloruro de metanosulfonilo (1.17 ml, 15.10 mmol), y se retiró el baño helado. Luego de agitar a temperatura de la sala durante 2 horas, la mezcla de reacción se lavó con agua (200 ml), se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 70:30 de heptano:EtOAc para producir el compuesto del título (1.8g, 53%) como una mezcla 50:50 de cis y trans isómeros. ^1H-NMR ($CDCl_3$, 500 MHz): δ 4.91-4.83 (m, 1H), 4.67-4.56 (m,1H), 4.53-4.31 (m, 2H), 3.58-3.36 (m, 2H), 3.00 (ds, 6H), 2.17-1.98 (m, 6H), 1.88-1.78 (m, 2H), 1.77-1.50 (m, 6H), 1.43 (ds, 18H), 1.33-1.18 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 155.4, 79.9, 78.1, 48.2, 39.0, 38.9, 31.3, 30.8, 30.0, 28.6, 27.7.

***terc*-Butil (4-{[4-(trifluorometil)fenil]tio}ciclohexil)carbamato**

4-[(*terc*-Butoxicarbonil)amino]ciclohexil metanosulfonato (0.7g, 2.39 mmol), 4-(trifluorometil)tiofenol (1.28g, 7.16 mmol) y K_2CO_3 (1.32g, 9.54 mmol) se disolvió en THF (21 ml), y la mezcla de reacción se calentó en un

reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se diluyó con agua (300 ml) y se extrajo con EtOAc (2x150 ml). Las fases orgánicas se secaron sobre Na_2SO_4, se filtraron y se evaporaron. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 85:15 de heptano:EtOAc para producir el compuesto del título (0.386g, 43%) como una mezcla 50:50 de cis y trans isómeros. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.55-7.50 (m, 4H), 7.45-7.40 (m, 4H), 4.70-4.23 (m, 2H), 3.69-3.36 (m, 3H), 3.16-3.05 (m, 1H), 2.13-2.04 (m, 4H), 1.95-1.64 (m, 9H), 1.54-1.40 (m, 1H), 1.45 (ds, 18H), 1.30-1.15 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 155.4, 141.1, 140.7, 130.5, 129.9, 128.6, 128.5, 128.2, 126.0, 125.9, 125.9, 125.9, 125.4, 123.2, 79.5, 49.1, 47.9, 44.8, 43.8, 33.4, 32.0, 29.2, 29.1, 28.6

(4-{[4-(Trifluorometil)fenil]tio}ciclohexil)amina

terc-Butil (4-{[4-(trifluorometil)fenil]tio}ciclohexil)carbamato (0.38g, 1.01 mmol) se disolvió en THF:MeOH 8:2 (10 ml), y se agregó HCl en 1,4-dioxano (4M, 2 ml). La mezcla de reacción se agitó a temperatura de la sala durante 15 horas, y luego se evaporó. El producto crudo se diluyó con EtOAc (100ml), se lavó con una mezcla de Na_2CO_3 acuoso saturado y agua (1:2, 100 ml) y agua (2x100 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar el compuesto del título (0.27g, 97%) como una mezcla 50:50 de cis y trans isómeros. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.56-7.48 (m, 4H), 7.46-7.39 (m, 4H), 3.59-3.52 (m, 1H), 3.17-3.07 (m, 1H), 2.90-2.79 (m, 1H), 2.78-2.68 (m, 1H), 2.13-2.03 (m, 2H), 1.99-1.14 (m, 18H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 141.6, 141.0, 130.2, 129.7, 125.9, 125.9, 50.0, 48.9, 45.0, 44.0, 36.6, 32.3, 32.1, 30.5, 29.2, 29.0, 28.6.

***terc*-Butil {1-[5-(trifluorometil)piridin-2-il]piperidin-4-il}carbamato**

Una mezcla de 2-cloro-5-(trifluorometil)piridina (1.00g, 5.51mmol), *terc*-butil 4-aminopiperidin-1-carboxilato (1.16g, 5.78mmol) y TEA (0.84ml, 6.06mmol) en DMSO (5ml) se calentó a 120°C durante 18 horas. La mezcla se evaporó, se agregó EtOAc, y la mezcla se lavó con agua, luego salmuera y se evaporó a sequedad. El producto crudo se purificó triturando con

MeOH y luego EtOAc para producir el compuesto del título (1.29g, 67%) como un sólido. ^{1}H-NMR (500MHz $CDCl_3$): 8.39 (s, 1H), 7.62 (dd, 1H), 6.66 (d, 1H), 4.48 (bs, 1H), 4.38-4.28 (m, 2H), 3.75 (bs, 1H), 3.07 (dt, 2H), 2.10-2.02 (m, 2H), 1.58-1.38 (m, HH); ^{13}C-NMR (125MHz $CDCl_3$): 160.3, 155.3, 146.0, 134.8, 125.9, 123.8, 115.3, 115.0, 105.8, 79.8, 48.3, 44.1, 32.3, 28.6; Espectro de Masa $M+H^+$ 346.

Diclorhidrato de 1-[5-(trifluorometil)piridin-2-il]piperidin-4-amina

Una mezcla de *terc*-butil {1-[5-(trifluorometil)piridin-2-il]piperidin-4-il}carbamato (1.27g, 3.68mmol) en HCl en dioxano/THF (4M, 1:1; 10ml) se agitó a temperatura de la sala. Luego de 6.5 horas, se agregó más HCl en dioxano (4M, 2ml), y la mezcla resultante se agitó durante 18 horas más. La mezcla se filtró, y el residuo se lavó con EtOAc para producir el compuesto del título (1.04g, 89%) como un sólido. ^{1}H NMR (500MHz CD_3OD): 8.35 (s, 1H), 8.20 (dd, 1H), 7.60 (d, 1H), 4.46 (d, 2H), 3.66-3.56 (m, 1H), 3.48 (td, 2H), 2.28 (d, 2H), 1.90-1.80 (m, 2H); ^{13}C NMR (125MHz CD_3OD): 153.5, 139.2, 136.3, 126.1, 123.9, 121.8, 120.0, 116.2, 115.9, 115.6, 115.3, 113.9, 45.2, 29.1; Espectro de Masa: $M+H^+$ 246.

***terc*-Butil 3-(cianometoxi)azetidin-1-carboxilato**

NaH (60% dispersión en aceite mineral, 276mg, 6.89mmol) se agregó a una solución helada de *terc*-butil 3-hidroxiazetidin-1-carboxilato (0.92mg, 5.30mmol) en THF (8mL) y se agitó durante 15 minutos. Se agregó gota a gota bromoacetonitrilo (0.52mL, 7.43mmol), y la mezcla de reacción se dejó calentar a temperatura de la sala. Luego de 2.5 horas, se agregó bromoacetonitrilo (0.074mL, 1.06mmol), y la mezcla de reacción se agitó a temperatura de la sala. Luego de 17 horas, se agregaron NaH (60% dispersión en aceite mineral, 0.085mg, 2.12mmol) y bromoacetonitrilo (0.074mL, 1.06mmol). Luego de 2 horas, la mezcla de reacción se evaporó a sequedad, y el producto crudo se purificó en un sistema HPFC Biotage Horizon, eluyendo con 5-90% EtOAc en éter de petróleo (40-60°C) para producir el compuesto del título (0.47g, 42%) como un aceite. ^{1}H NMR($CDCl_3$): δ 4.46-4.40 (m, 1H), 4.24 (s, 2H), 4.17 (dd, 2H), 3.92 (dd,

2H), 1.45 (s, 9H); ^{13}C NMR(CDCO): δ 156.3, 115.6, 80.2, 69.3, 56.3, 54.6, 28.6.

***terc*-Butil 3-(2-aminoetoxi)azetidin-1-carboxilato**

Una mezcla de *terc*-butil 3-(cianometoxi)azetidin-1-carboxilato (0.46g, 2.19 mmol) y 10% Pd/C (10%) en EtOH se agitó bajo gas H_2 a 3 atmósferas. Luego de 3 horas, la mezcla de reacción se filtró a través de celita, y el filtrado se evaporó a sequedad para producir el compuesto del título (0.41g, 87%) como un aceite. ^{1}HNMR($CDCl_3$): δ 4.27-4.20 (m, 1H), 4.08 (t, 2H), 3.84 (dd, 2H), 3.49 (t, 2H), 2.84 (t, 2H), 1.45 (s, 9H); ^{13}C NMR(CDCl3): δ 156.6, 79.7, 68.3, 68.2, 56.7, 49.4, 28.6.

2-[4-(Trifluorometoxi)fenil]acetamida

ácido 4-(trifluorometoxi)fenilacético (2 g, 9.085 mmol) se disolvió en DMF (20 ml, seco), y se agregó PyBOP (4.728 g, 9.085 mmol). La mezcla se agitó en un baño helado, y se hizo burbujear gas amoníaco durante 5 minutos. El baño helado se retiró, y la mezcla se agitó a temperatura de la sala de un día para otro y, a continuación, se evaporó *in vacuo*. Se agregó agua (50 ml) en el residuo y se extrajo con EtOAc (20 ml x3). Los extractos se combinaron, se lavaron con $NaHCO_3$ acuoso saturado (15 ml), agua (20 ml x3), salmuera (15 ml), se secaron ($MgSO_4$) y se evaporaron. El residuo se purificó por cromatografía en columna (ISOLUTE SI, 20g/70 ml), eluyendo con DCM, luego MeOH/DCM (1:99), para producir el compuesto del título (1.14 g, 57%) como un sólido blanco. Espectro de Masa: M-H$^+$ 218. ^{1}H NMR (400 MHz, CD_3OD): δ 3.53 (s, 2H), 7.20 (d, 2H), 7.38 (d, 2H). ^{13}C NMR (100 MHz, CD_3OD): 42.5, 121.9 (q, J=253 Hz), 122.1, 131.8, 136.3, 149.4, 176.2.

2-[4-(Trifluorometoxi)fenil]etanamina

2-[4-(Trifluorometoxi)fenil]acetamida (1.13 g, 5.156 mmol) se disolvió en THF (20 ml), y la mezcla de reacción se enfrió en un baño helado. Complejo sulfuro de dimetilo - borano (6.4 ml, 2M en THF) se agregó gota a gota. Luego de la adición, se retiró el baño de enfriamiento, y la mezcla se calentó a reflujo durante 5 horas y se enfrió a temperatura de la sala. Se agregó HCl (10 %, 4 ml), la mezcla se agitó a temperatura de la sala de un

día para otro y luego se evaporó para retirar THF. Agua (15 ml) y éter dietílico (15 ml) se agregaron en el residuo. Las dos fases se separaron, se agregó $NaHCO_3$ (saturado) en la fase acuosa. Se extrajo luego con EtOAc (20 ml x3). Los extractos se combinaron y se lavaron con salmuera, se secaron (Na_2SO_4) y se evaporaron. El residuo se purificó por cromatografía en columna (ISOLUTE SI, 20g/70 ml), eluyendo con MeOH/DCM (1:99, 2:98, 5:95 luego 10:90), para producir 0.2 g del producto deseado y 0.46 g de mezcla. La mezcla se purificó posteriormente por re-cromatografía (ISOLUTE SI, 20g/70 ml), eluyendo con MeOH/EtOAc (2:98, 5:95, 10:90), para producir 0.107g más del producto deseado. En total se obtuvo (0.307g, 29%) del compuesto del título. Espectro de Masa: $M+H^+$ 206. ^1H NMR (400 MHz, CD_3OD): δ 2.95 (t, 2H), 3.12 (t, 2H), 7.23 (d, 2H), 7.38 (d, 2H). ^{13}C NMR (100 MHz, CD_3OD): 35.3, 42.5, 122.2 (q, J=250 Hz), 122.6, 131.7, 136.2, 149.7.

***terc*-Butil-(2-{[5-(trifluorometil)piridin-2-il]oxi}-etil)carbamato**

terc-Butil (2-hidroxietil)carbamato (8.88g, 55.08mmol) se agregó a una solución de NaH (55%, 55.08mmol, lavado dos veces con éter de petróleo) en DMF (150ml) a -10°C y se agitó durante 10minutos. Se agregó 2-cloro-5-(trifluorometil)piridina (10.0g, 55.08mmol), y luego la mezcla de reacción se agitó a temperatura de la sala durante 3 días, se calentó a 100°C y se enfrió a temperatura de la sala. La mezcla de reacción se evaporó, el residuo se lavó con éter isopropílico, y la solución se decantó de sales insolubles y se concentró. El residuo se disolvió en EtOAc, se lavó dos veces con agua, se secó sobre $MgSO_4$ y se concentró. La recristalización de isobutiletil éter produjo el compuesto del título (6.2g, 37%). ^1H-NMR (500MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.56 (br.m, 2H), 4.45 (t, 2H), 6.84 (d, 1H), 7.79 (dd, 1H), 8.44 (s, 1H).

Clorhidrato de 2-{[5-trifluorometil)piridin-2-il]oxi}etil)amina

terc-Butil-(2-{[5-(trifluorometil)piridin-2-il]oxi}-etil)carbamato (6.1g, 19.92mmol) en EtOAc (saturado con HCl) se agitó durante 2 días. La mezcla de reacción se concentró suficientemente para precipitación del

compuesto del título (4.7g) como la sal HCl. ^{1}H-NMR (300MHz, CD_3OD): δ 3.39 (t, 2H), 4.64 (t, 2H), 7.04 (d, 1H), 7.99 (dd, 1H), 8.5 (s, 1H).

terc-Butil (1-piridin-2-ilazetidin-3-il)carbamato

El compuesto del título se preparó de 2-cloropiridina y *terc*-butil azetidin-3-ilcarbamato en una manera similar a la descrita para *terc*-butil {1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-il}carbamato. ^{1}H NMR (500MHz $CDCl_3$): δ 1.46 (s, 9H), 3.76-3.80 (m, 2H), 4.31-4.35 (m, 2H), 4.63 (bs, 1H), 5.10 (bs, 1H), 6.29 (d, 1H), 6.61-6.64 (m, 1H), 7.43-7.47 (m, 1H), 8.14-8.16 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 28.58, 41.79, 58.58, 80.22, 106.36, 113.48, 137.37, 148.42, 155.24, 160.66; Espectro de Masa: $M+H^+$ 250.

l-Piridin-2-ilazetidin-3-amina

El compuesto del título se preparó de *terc*-butil (1-piridin-2-ilazetidin-3-il)carbamato en una manera similar a la descrita para 1-[3-cloro-5-(trifluorometil) piridin-2-il]azetidin-3-amina. ^{1}H NMR (500MHz $CDCl_3$): δ 1.96 (bs, 2H), 3.59-3.63 (m, 2H), 3.89-3.95 (m, 1H), 4.22-4.27 (m, 2H), 6.26 (d, 1H), 6.55-6.58 (m, 1H), 7.38-7.43 (m, 1H), 8.11 (s, 1H).

2,6-Dimetilfenil 4-[(_terc_-butoxicarbonil)amino]butanoato

2,6-Dimetilfenol (0.257 g, 2.1 mmol) y ácido 4-[(*terc*-butoxicarbonil) amino]butanoico (0.427 g, 2.1 mmol) se disolvieron en THF (10 ml, seco), se agregó y DMAP (0.005 g, 0.04 mmol). Luego de enfriar a 0-2 °C, se agregó EDC (0.483 g, 2.52 mmol) en porciones bajo una atmósfera de nitrógeno. El baño helado se retiró, y se continuó la agitación de un día para otro a temperatura de la sala. Luego de 17 horas, la mezcla se diluyó con DCM (50 ml) y se extrajo con agua (20 ml), HCl (2N, 20 ml) y agua (20 ml) nuevamente. La capa orgánica se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía en columna en gel de sílice, usando DCM / MeOH (95:5) como eluyente, para producir el compuesto del título (0.493 g, 76%) como un sólido incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s 9H), 1.94-2.01 (m, 2H), 2.14 (s, 6H), 2.66 (t, 2H), 3.24-3.29 (m, 2H), 4.66 (bs, 1H), 7.05 (s, 3H); Espectro de Masa: M-*terc*-Bu + H^+ 252.1

Clorhidrato de 2,6-dimetilfenil 4-aminobutanoato

2,6-Dimetilfenil 4-[(*terc*-butoxicarbonil)amino]butanoate (0.49 g, 1.594 mmol) se disolvió en DCM (20 ml), y HCl (4M in dioxane, 1.2 ml) se agregó gota a gota a 0 °C. La mezcla se agitó durante 30 minutos a 0-2 °C antes de retirar el baño helado, y se continuó la agitación a temperatura de la sala. La mezcla se evaporó *in vacuo* para producir el compuesto del título (0.371 g, 86%) como un sólido blanco. Éste se utilizó sin purificación posterior. ^{1}H NMR (400 MHz, DMSO-d6): δ 1.88-1.96 (m, 2H), 2.07 (s, 6H), 2.80 (t, 2H), 2.85 (bs, 2H), 7.02-7.11 (m, 3H), 8.10 (bs, 3H).

Fenil N-(*terc*-butoxicarbonil)-β-alaninato

El compuesto del título se preparó de *N*-(*terc*-butoxicarbonil)-β-alanina y fenol en una manera similar a la descrita para 2,6-dimetilfenil 4-[(*terc*-butoxicarbonil)amino]butanoato. Espectro de Masa (M-*terc*-Bu) + H^+ 211.09.

Clorhidrato de fenil β-alaninato

El compuesto del título se preparó de fenil *N*-(*terc*-butoxicarbonil)-β-alaninato en una manera similar a la descrita para clorhidrato de 2,6-dimetilfenil 4-aminobutanoato. ^{1}H NMR (400 MHz, CDCl3): δ 7.36-7.40 (t, 2H), 1.22-1.25 (t, 1H), 7.12-7.14 (d, 2H), 4.82 (s, 3H), 3.27-3.30 (m, 2H), 2.99-3.03 (t, 2H).

4-(Trifluorometoxi)fenil *N*-(*terc*-butoxicarbonil)-β-alaninato

El compuesto del título se preparó de *N*-(*terc*-butoxicarbonil)-β-alanina y 4-(trifluorometoxi)fenol en una manera similar a la descrita para 2,6-dimetilfenil 4-[(*terc*-butoxicarbonil)amino]butanoato. Espectro de Masa (M-*terc*-Bu) + H^+ 293.96

4-(Trifluorometoxi)fenil β-alaninato

El compuesto del título se preparó de 4-(trifluorometoxi)fenil *N*-*terc*-butoxicarbonil)-β-alaninato en una manera similar a la descrita para clorhidrato de 2,6-dimetilfenil 4-aminobutanoato. Espectro de Masa M + H^+ 251.10

1-Metilpiperidin-4-il *N*-(*terc*-butoxicarbonil)-β-alaninato

El compuesto del título se preparó de 1-metilpiperidin-4-ol y *N*-(*terc*-butoxicarbonil)-β-alanina en una manera similar a la descrita para 2,6-dimetilfenil 4-[(*terc*-butoxicarbonil)amino]butanoato. ^{1}H NMR (400 MHz, CDCl3): δ 4.99 (s, 1H), 4.74-4.79 (m, 1H), 3.32-3.6 (m, 2H), 2.58 (s, 2H), 2.45-2.49 (t, 2H), 2.23 (s, 3H), 2.16-2.19 (m, 2H), 1.83- 1.88 (m, 2H), 1.62-1.71 (m, 2H), 1.34 (s, 9H).

Clorhidrato de 1-metilpiperidin-4-il β-alaninato

El compuesto del título se preparó de 1-metilpiperidin-4-il *N*-(*terc*-butoxicarbonil)-β-alaninato en una manera similar a la descrita para clorhidrato de 2,6-dimetilfenil 4-aminobutanoato. Espectro de Masa M + H^+ 188.17.

Mesitilacetaldehído

2-Mesitiletanol (0.99g, 6.0mmol) se disolvió en DCM (10.0mL, seco) y se enfrió a 0°C. 1,1,1-Tris(acetiloxi)-1λ^5,2-benziodoxol-3(1H)-ona (periodinano de Dess-Martin) en DCM (15 % en peso, 2.80g, 6.60mmol) se agregó gota a gota durante un período de 20 minutos. El baño helado se retiró, y la mezcla de reacción se agitó a temperatura de la sala durante 4 horas. NaOH (2N, 5mL) se agregó a la mezcla y se diluyó con agua (5mL). Las capas se separaron, y la capa orgánica se lavó con agua, se secó sobre Na_2SO_4, y se evaporó. El residuo se purificó por cromatografía en columna en gel de sílice usando heptano y EtOAc como eluyente, produciendo el compuesto del título (0.69g, 71%). ^{1}H NMR ($CDCl_3$, 400MHz) δ 9.68-9.65 (m, 1H), 6.94-6.90 (m, 2H), 3.75-3.71 (m, 2H), 2.29 (s, 3H), 2.27 (s, 6H).

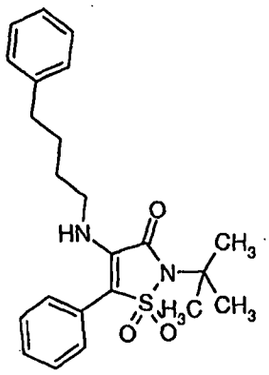
1-Mesitilpropan-2-ol

Mesitilacetaldehído (0.68g, 4.19mmol) se disolvió en THF (5.0mL, seco), y MeMgBr en Et_2O (3.0M, 0.75g, 6.29mmol)) se agregó lentamente a 0°C. El baño de enfriamiento se retiró, y la mezcla de reacción se agitó a temperatura de la sala durante 4.5 horas. La mezcla se enfrió a 0°C, y el exceso de reactivo de Grignard se hidrolizó con HCl (1N). La mezcla se diluyó con agua y se extrajo con Et_2O. La capa orgánica se secó sobre Na_2SO_4, se evaporó, y el residuo se purificó por cromatografía en columna en gel de sílice usando MTBE, heptano y DCM como eluyente,

produciendo el compuesto del título (0.51g, 61%). ^{1}H NMR ($CDCl_3$, 500MHz) δ 6.88-6.85 (m, 2H), 4.08-3.99 (m, 1H), 2.87-2.72 (m, 2H), 2.32 (s, 6H), 2.26 (s, 3H), 1.29 (d, 3H).

Ejemplo 1

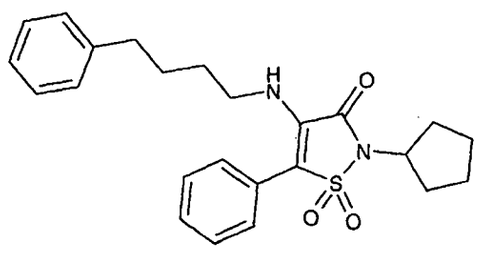
1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona



Una solución de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.150g, 0.50mmol), TEA (0.076g, 0.751mmol) y 4-fenilbutilamina (0.097g, 0.65mmol) en MeCN (3mL) se calentó en un reactor microondas a 120°C durante 10 minutos. La mezcla se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 85:15 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.19g, 92%) como un sólido; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52-1 A1 (m, 2H), 7.45-7.40 (m, 3H), 7.31-7.26 (m 2H), 7.22-7.17 (m, 1H), 7.08 (d, 2H), 5.26 (t, 1H), 2.88-2.81 (m, 2H), 2.49-7.43 (m 2H), 1.75 (s 9H), 1.48-1.36 (m 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 141.8, 135.3, 131.9, 129.8, 128.8, 128.6, 128.5, 126.2, 125.3, 107.0, 61.7, 44.1, 35.5, 29.2, 28.4, 27.9; Espectro de Masa: M-H^+ 413.

Ejemplo 2

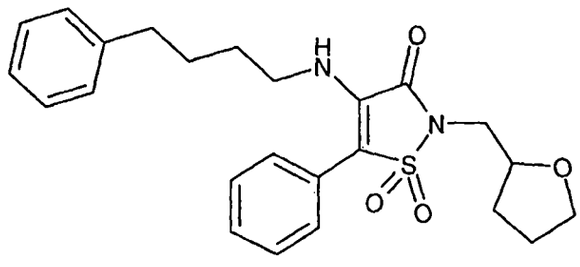
1,1-Dióxido de 2-ciclopentil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona



1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona (Ejemplo 1) (0.150g, 0.364mmol) se disolvió en TFA (3mL) y se calentó en un reactor microondas a 120°C durante 20 minutos. TFA se retiró *in vacuo*, y el residuo se co-evaporó con DCM dos veces. El residuo se disolvió en MeCN (3mL) y se mezcló con bromociclopentano (0.162g, 1.09mmol) y TEA (0.110g, 1.09mmol), y la mezcla se calentó en un reactor microondas a 120°C durante 20 minutos, a 160°C durante 85 minutos y a 170 °C durante 20 minutos. El residuo se purificó por cromatografía en columna (Horizons Biotage) usando una mezcla 90:10 de hexano y EtOAc como eluyente, para producir el compuesto del título (0.055 g, 36%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.48 (m, 2H), 7.46-7.41 (m, 3H), 7.31-7.25 (m 2H), 7.22- 7.18 (m, 1H), 7.10-7.06 (m, 2H), 5.30-5.24 (br m, 1H), 4.41-4.35 (m, 1H), 2.90-2.83 (m 2H), 2.49-2.43 (m 2H), 2.25-2.17 (m 2H), 2.18-2.09 (m 2H), 1.97-1.87 (m 2H), 1.69-1.60 (m 2H), 1.44-1.36 (m 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 141.8, 135.6, 131.8, 129.8, 128.8, 128.6, 128.5, 126.2, 125.3, 106.7, 55.2, 44.2, 35.4, 29.5, 29.2, 28.3, 24.3.

Ejemplo 3

1,1-Dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(tetrahidrofuran-2-ilmetil)isotiazol-3(2*H*)-ona

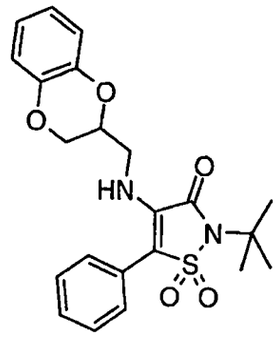


1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona (Ejemplo 1) (0.150g, 0.364mmol) se disolvió en TFA (3mL) y se calentó en un reactor microondas a 120°C durante 20 minutos. TFA se retiró *in vacuo* y se co-evaporó con DCM dos veces. El residuo se disolvió en MeCN (3mL) y se mezcló con 2-(bromometil)tetrahidrofurano (0.312g, 1.892mmol), TEA (0.148g, 1.454mmol) y K_2CO_3 (0.251g, 1.818mmol), y se calentó en un reactor microondas a 140°C durante 15 minutos y a 160°C durante 80 minutos. El residuo se purificó por cromatografía en columna

(Horizons Biotage) usando una mezcla 75:25 de hexano y EtOAc como eluyente, para producir el compuesto del título (0.055g, 36%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H), 7.46-7.41 (m, 3H), 7.31-7.25 (m 2H), 7.22-7.18 (m, 1H), 7.10-7.06 (m, 2H), 5.30-5.24 (br m, 1H), 4.42-4.36 (m, 1H), 4.00-3.95 (m, 1H), 3.86-3.79 (m 2H), 3.72-3.65 (dd, 1H), 2.91-2.83 (m 2H), 2.49-2.43 (m 2H), 2.14-2.06 (m, 1H), 2.06-1.89 (dm 2H), 1.77-1.68 (m, 1H), 1.44-1.36 (m 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 141.7, 135.6, 131.9, 129.9, 128.8, 128.6, 128.5, 126.2, 125.1, 107.0, 68.5, 44.2, 35.4, 29.6, 29.2, 28.3, 25.7; Espectro de Masa: M-H$^+$ 425.

Ejemplo 4

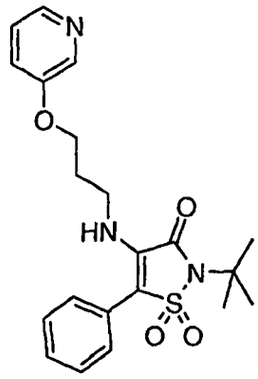
1,1-Dióxido de 2-*terc*-Butil-4-[(2,3-dihidro-1,4-benzodioxin-2-ilmetil) amino]-5-fenilisotiazol- 3(2*H*)-ona



Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.150g, 0.50mmol) y (2,3-dihidro-1,4-benzodioxin-2-ilmetil)amina (0.083g, 0.50mmol) y TEA (0.07mL, 0.50mmol) en MeCN (2mL) se calentó en un reactor microondas a 100°C durante 45 minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice usando a 15-25% EtOAc en mezcla de éter de petróleo como eluyente, para producir el compuesto del título (0.139g, 65%) como un sólido; ^{1}H NMR (500 MHz, CDCl3): δ 7.54-7.50 (m, 2H), 7.50-7.45 (m, 3H), 6.92-6.82 (m, 4H), 5.65 (t, 1H), 4.12-4.04 (m, 1H), 3.86 (dd, 1H), 3.68 (dd, 1H), 3.17 (t, 2H), 1.75 (s, 9H); ^{13}C NMR (125 MHz, CDCl3): δ 159.5, 142.9, 142.3, 135.1, 131.7, 130.2, 129.2, 124.8, 122.2, 122.1, 117.7, 117.5, 108.7, 71.4, 65.3, 61.9, 44.1, 27.9; Espectro de Masa: [M+H]$^+$ 429.

Ejemplo 5

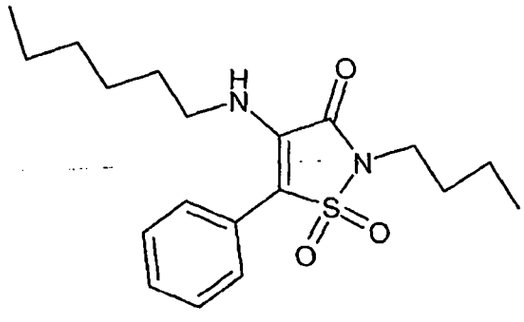
1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-3-iloxi)propil]amino} isotiazol-3(2*H*)-ona



Una mezcla de 1,1-dióxido de 4-[(3-bromopropil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona (0.120g, 0.29mmol), 3-hidroxipiridina (0.028g, 0.29mmol) y K_2CO_3 (0.207g, 1.49mmol) en MeCN (2mL) se calentó en un reactor microondas a 140°C durante 30 minutos. El disolvente se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 35-85% EtOAc en hexano como eluyente, para producir el compuesto del título (0.056g, 45%) como un sólido. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28-8.22 (m, 2H), 7.54-7.50 (m, 2H), 7.50-7.42 (m, 3H), 7.24-7.20 (m, 1H), 7.16-7.12 (m, 1H), 5.68 (t, 1H), 3.92 (t, 2H), 3.14-3.08 (m, 2H), 1.90-1.82 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 154.7, 142.8, 137.9, 135.2, 131.8, 129.9, 128.8, 125.2, 124.1, 121.3, 107.5, 66.3, 61.8, 42.1, 29.0, 27.8; Espectro de Masa: $M+H^+$ 416.

Ejemplo 6

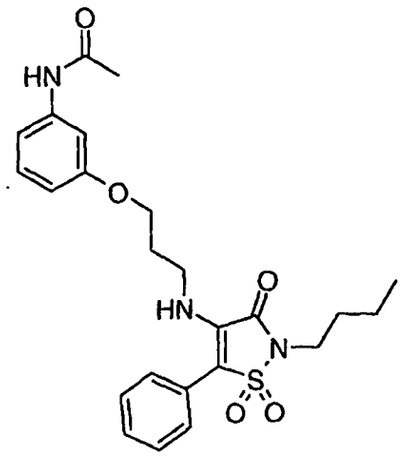
1,1-Dióxido de 2-butil-4-(hexilamino)-5-fenilisotiazol-3(2*H*)-ona



Una solución de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.110g, 0.33mmol) y hexilamina (0.100g, 0.984mmol) en DMF (0.5mL) se calentó en un reactor microondas a 140°C durante 25 minutos. El residuo se purificó por HPLC preparativa (columna Ace C8, 0.1M NH_4OAcMeCN, gradiente) para producir el compuesto del título (0.060g, 47%); ^{1}H-NMR (400 MHz, CD_3CN): δ 7.49-7.53 (m, 5H), 5.85 (bs, 1H), 3.66 8(t, 2H), 2.85 (dd, 2H), 1.71-1.80 (m, 2H), 1.37-1.48 (m, 2H), 1.13-1.34 (m, 4H), 0.94-1.09 (m, 7H), 0.82 (t, 3H); Espectro de Masa: M+H 365.

Ejemplo 7

N-(3-{3-[(2-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetamida

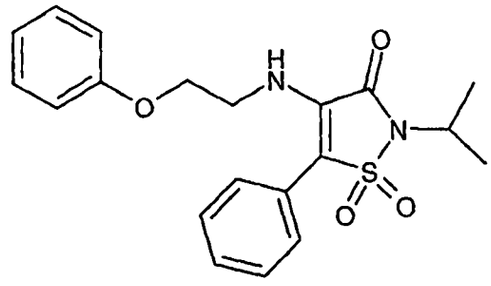


Una mezcla de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.150g, 0.50mmol) y 3-(3-aminopropiloxi)acetanilida (0.208mg, 1.00mmol) en MeCN (2mL) se calentó en un reactor microondas a 120°C durante 15 minutos. La mezcla de reacción se filtró, y el residuo sólido se lavó con EtOAc. El filtrado se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice usando 50-100 % EtOAc en mezcla de éter de petróleo como eluyente, para producir el compuesto del título (0.148g, 63%) como un sólido; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.52 (m, 2H), 7.50-7.44 (m, 3H), 7.22 (t, 1H), 7.18 (br s, 1H), 6.96 (dd, 1H), 7.64 (dd, 1H), 5.82 (t, 1H), 3.92 (t, 2H), 3.72 (t, 2H), 3.18-3.06 (m, 2H), 2.20 (s, 3H), 1.88-1.80 (m, 4H), 1.50-1.40 (m, 2H), 0.98 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 159.2, 159.0, 139.6, 135.8, 131.7, 130.0,

129.0, 128.9, 125.0, 112.4, 110.8, 106.1, 66.2, 42.7, 40.4, 30.5, 28.9, 25.2, 20.3, 13.8; Espectro de Masa: $[M+H]^+$ 472.

Ejemplo 8

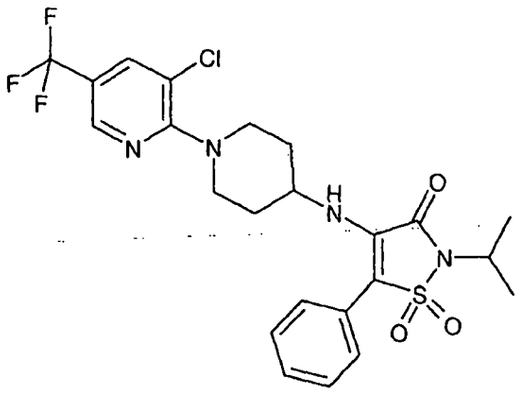
1,1-Dióxido de 2-isopropil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona



Una solución de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.200g, 0.700mmol), TEA (0.106g, 1.050mmol) y 2-fenoxietilamina (0.144g, 1.050mmol) en MeCN (3mL) se calentó en un reactor microondas a 120°C durante 5 minutos. El residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando una mezcla 65:35 de heptano y EtOAc como eluyente para producir el compuesto del título (0.262g, 97%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.49-7.45 (m, 3H), 7.32-7.27 (m, 2H), 7.02-6.97 (m, 1H), 6.86-6.83 (m, 2H), 5.71-5.66 (br m, 1H), 4.46-4.39 (m, 1H), 3.89 (t 2H), 3.27 (q 2H), 1.60 (d 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 158.2, 135.6, 131.7, 130.0, 129.8, 129.1, 125.1, 121.8, 10 114.7, 108.0, 65.8, 47.8, 43.6, 20.4; Espectro de Masa: $M-H^+$ 387.

Ejemplo 9

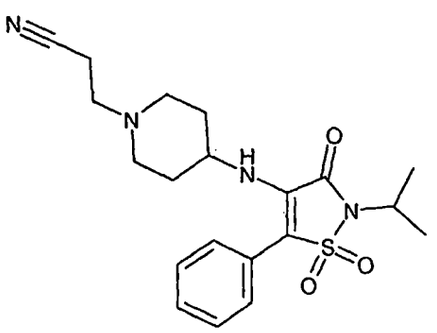
1,1-Dióxido de 4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il}amino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona



Una solución de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.200g, 0.700mmol), TEA (0.106g, 1.050mmol) y 1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-amina (0.294g, 1.050mmol) en MeCN (mL) se calentó en un reactor microondas a 120°C durante 30 minutos. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando una mezcla 1:1 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.344 g, 93 %); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34-8.33 (m, 1H), 7.74-7.72 (m, 1H), 7.57-7.54 (m, 2H), 7.49-7.46 (m, 3H), 5.27 (d, 1H), 4.47-4.39 (m, 1H), 3.85-3.78 (m, 2H), 3.24-3.14 (m, 1H), 2.55-2.48 (m 2H), 1.82-1.76 (m 2H), 1.60 (d, 6H), 1.56-1.48 (m 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 158.7, 143.1, 136.2, 134.5, 131.8, 130.2, 129.0, 125.3, 121.3, 120.6, 120.3, 107.1, 66.1, 50.3, 47.9, 47.4, 32.4, 20.4; Espectro de Masa: M-H$^+$ 529.

Ejemplo 10

3-{4-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}propanonitrilo



Una solución de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.200g, 0.700mmol), TEA (0.283g, 2.800mmol) y 3-(4-

aminopiperidin-1-il)propanonitrilo (0.161g, 1.050mmol) en DMF (3mL) se calentó en un reactor microondas a 120°C durante 10 minutos. Se agregó agua, y la mezcla se extrajo con EtOAc. La fase orgánica se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando una mezcla de heptano y EtOAc (20:80) a 100% EtOAc, luego una mezcla de MeOH y EtOAc (1:99) como eluyente, para producir el compuesto del título (0.25g, 89%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H), 7.49-7.44 (m, 3H), 5.20 (br d IH), 4.46-4.38 (m, 1H), 3.01-2.91 (br m, 1H), 2.70-2.65 (br m, 2H), 2.55 (t, 2H), 2.41 (t 2H), 1.74-1.63 (m 4H), 1.60 (d 6H) 1.44-1.35 (m 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 134.5, 131.8, 130.1, 128.9, 125.3, 118.8, 106.8, 53.3, 51.5, 50.0, 47.8, 32.4, 20.4, 16.4: Espectro de Masa: M-H^+ 403.

Ejemplo 11

1,1-Dióxido de 2-isopropil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

Una solución de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.150g, 25 0.521mmol), TEA (0.079g, 0.782mmol) y 4-fenilbutilamina (0.117g, 0.782mmol) en MeCN (3mL) se calentó en un reactor microondas a 120°C durante 5 minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando una mezcla 75:25 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.174 g, 84 %); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.45-7.41 (m, 3H), 7.30-7.26 (m, 2H), 7.22-7.17 (m, 1H), 7.10-7.06 (m, 2H), 5.28-5.23 (m, 1H), 4.45-4.38 (m, 1H), 2.89-2.84 (m, 2H), 2.49-2.44 (m, 2H), 1.59 (d, 6H), 1.43-1.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 141.8, 135.6, 131.8, 129.8, 128.8, 128.6, 128.5, 126.2, 125.3, 106.8, 47.7, 44.2, 35.4, 29.2, 28.3, 20.4; Espectro de Masa: M-H^+ 399.

Ejemplo 12

1,1-Dióxido de2-*terc*-butil-4-({3-[3-(hidroximetil)fenoxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

Una mezcla de 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato (0.120g, 0.244mmol), 3-(hidroximetil)fenol (0.030mg, 0.244mmol) y K_2CO_3 (0.168mg, 1.218mmol) en MeCN (2ml) se calentó en el reactor microondas a 120°C durante 25minutos. La mezcla de reacción se filtró, se evaporó, y el residuo se purificó dos veces por cromatografía en columna en gel de sílice (Horizons Biotage) usando 50% EtOAc en hexano y luego 0-10%EtOAc en DCM como eluyente para producir el compuesto del título (0.049mg, 45%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.7.46 (m, 2H), 7.45-7.40 (m, 3H), 7.30-7.24 (m, 1H), 6.96 (d, 1H), 6.91 (s, 1H), 6.78 (d, 1H), 5.73 (t, 1H), 4.69 (s, 2H), 3.92 (t, 2H), 3.11-3.06 (m, 2H), 1.88-1.80 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 158.8, 142.9, 135.4, 131.8, 129.9, 129.8, 128.8, 125.3, 119.8, 113.9, 112.9, 107.2, 66.0, 65.4, 61.7, 42.4, 28.9, 27.8; Espectro de Masa $M+H^+$ 445.

Ejemplo 13

1,1-Dióxido de 2-*terc*-butil-4-{[3-(2-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 2-metoxifenol y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 15minutos. Se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 15% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.077mg, 72%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.43-7.40 (m, 3H), 6.97-6.94 (m, 1H), 6.92-6.88 (m, 2H), 6.81(dd, 1H), 5.88 (t, 1H), 3.94 (t, 2H), 3.89 (s, 3H), 3.14-3.09 (m, 2H), 1.88-1.84 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 149.9, 148.1, 135.6, 131.8, 129.7, 128.8, 125.5,

121.9, 120.9, 113.8, 111.9, 106.9, 67.5, 61.6, 55.9, 42.6, 29.1, 27.9; Espectro de Masa $M+H^+$ 445.

Ejemplo 14

1,1-Dióxido de 2-*terc*-butil-4-({3-[4-(hidroximetil)fenoxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 4-(hidroximetil)fenol y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato. Se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 0-10% EtOAc en DCM como eluyente para producir el compuesto del título (0.037mg, 34%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.48 (m, 2H), 7.46-7.40 (m, 3H), 7.29 (d, 2H), 6.85 (d, 2H), 5.74 (t, 1H), 4.64 (s, 2H), 3.90 (t, 2H), 3.11-3.00 (m, 2H), 1.87-1.82 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 158.2, 135.3, 133.8, 131.8, 129.8, 128.9, 128.8, 125.3, 114.7, 107.2, 66.1, 65.2, 61.7, 42.5, 28.9, 27.8, Espectro de Masa $M+H^+$ 445.

Ejemplo 15

N-(3-{3-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetamida

Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.150g, 0.500mmol) y 3-(3-aminopropiloxi)acetanilida (0.208g, 1.000mmol) en MeCN (2ml) se calentó en un reactor microondas a 120°C durante 15minutos. La mezcla se evaporó, y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 50-65% EtOAc en hexano como eluyente para producir el compuesto del título (0.204mg, 87%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.48-7.42 (m, 3H), 7.30-7.24 (m, 1H), 7.24-7.18 (m, 2H), 6.94 (dd, 1H), 6.62 (dd, 1H), 5.69 (t, 1H), 3.88 (t, 2H), 3.12-3.04 (m, 2H), 2.18 (s, 3H), 1.86-1.80 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 168.4, 160.0,

159.4, 139.8, 135.8, 131.8, 129.9, 129.8, 128.8, 125.6, 112.4, 110.9, 106.1, 66.0, 61.8, 42.3, 28.9, 27.8, 25.2; Espectro de Masa $M+H^+$ 472.

Ejemplo 16

1,1-Dióxido de 2-*terc*-butil-4-{[3-(2-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 2-fluorofenol y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 15 minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 15% EtOAc en éter de petróleo 40-60°C como eluyente, luego se disolvió en EtOAc. El producto que contenía las fracciones se evaporó, y el residuo se lavó con K_2CO_3 acuoso (2M) y se evaporó para producir el compuesto del título (0.063g, 62%). ^1H NMR (500MHz $CDCl_3$): δ 7.54- 7.50 (m, 2H), 7.45-7.40 (m, 3H), 7.11-7.03 (m, 2H), 6.94-6.85 (m, 2H), 5.57 (t, 1H), 3.91 (t, 2H), 3.15-3.10 (m, 2H), 1.90-1.82 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 153.9, 152.0, 146.8, 146.7, 135.3, 131.8, 129.8, 128.8, 125.2, 124.6, 124.5, 121.9, 121.8, 116.6, 116.5, 115.5, 107.4, 67.2, 61.7, 41.7, 29.2, 27.8. Espectro de Masa $M+H^+$ 433.

Ejemplo 17

2-(4-{3-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)-N,N-dimetilacetamida

El compuesto del título se preparó como se describe para Ejemplo 12 de 2-(4-hidroxifenil)-*N*,*N*-dimetilacetamida y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato. La mezcla de reacción se evaporó, se purificó dos veces por cromatografía en columna en gel de sílice (Horizons Biotage) usando 75-20 85% EtOAc en éter de petróleo 40-60°C y luego 50% DCM en EtOAc como eluyente para producir el compuesto del título (0.072g, 59%). ^1H NMR (500MHz $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.46-7.42 (m, 3H), 7.18 (d, 2H), 6.82 (d, 2H), 5.76 (t,

1H), 3.87 (t, 2H), 3.66 (s, 2H), 3.08 (m, 2H), 3.01 (s, 3H), 2.98 (s, 3H), 1.83 (m, 2H), 1.74 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.5, 159.8, 157.4, 135.3, 131.8, 130.1, 129.7, 128.8, 127.8, 125.3, 114.8, 107.1, 66.1, 61.7, 42.5, 40.3, 37.9, 35.9, 28.9, 27.8; Espectro de Masa $M+H^+$ 500.

Ejemplo 18

1,1-Dióxido de 2-*terc*-butil-4-{[3-(2-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 2-clorofenol y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 15minutos. La mezcla de reacción se evaporó, y el producto crudo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 15% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.085g, 77%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.53-7.50 (m, 2H), 7.44-7.42 (m, 3H), 7.36 (dd, 1H), 7.19 (dt, 1H), 7.6.92 (dt, 1H), 6.83 (dd, 1H), 5.56 (t, 1H), 3.89 (t, 2H), 3.28 (m, 2H), 1.88-1.84 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 154.2, 135.3, 131.8, 130.6, 129.8, 128.8, 127.9, 125.2, 123.4, 122.1, 113.7, 107.4, 66.7, 61.7, 41.8, 29.2, 27.8; Espectro de Masa $M+H^+$ 449.

Ejemplo 19

1,1-Dióxido de 2-*terc*-butil-4-{[3-(3-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 3-metoxifenol y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 15minutos. La mezcla de reacción se evaporó, y el producto crudo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 15% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.070g, 65%). ^{1}HNMR (500MHz $CDCl_3$): δ 7.54-7.45 (m, 2H), 7.45 (m, 3H), 7.18 (t, 1H), 6.53 (dd, 1H),

6.48-6.42 (m, 2H), 5.79 (t, 1H), 3.89 (t, 2H), 3.82 (s, 3H), 3.12-3.06 (m, 2H), 1.86-1.82 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 161.1, 159.8, 159.7, 135.3, 131.8, 130.2, 129.7, 128.8, 125.3, 107.2, 107.1, 106.6, 101.2, 66.2, 61.7, 55.5, 42.6, 28.9, 27.8; Espectro de Masa $M+H^+$ 445.

Ejemplo 20

Ácido (3-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acético

Una mezcla de metil (3-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato (Ejemplo 21) (0.087g, 0.179mmol) y LiI (0.239g, 1.788mmol) en piridina (2ml) se calentó a 120°C durante 18 horas. EtOAc se agregó, y la mezcla se lavó con 1N HCl, se evaporó a sequedad, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 0-12% MeOH (+1% AcOH) en EtOAc como eluyente para producir el compuesto del título (0.033g, 39%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.46 (m, 2H), 7.45-7.40 (m, 3H), 7.25 (t, 1H), 6.89 (dd, 1H), 6.82-6.75 (m, 2H), 5.73 (t, 1H), 3.87 (t, 2H), 3.63 (s, 2H), 3.10-3.04 (m, 2H), 1.87-1.79 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 176.7, 159.8, 158.7, 135.4, 135.0, 131.8, 129.9, 129.8, 128.8, 125.3, 122.4, 115.7, 113.6, 107.2, 65.9, 61.7, 42.3, 41.2, 29.0, 27.8; Espectro de Masa: $M2H^+$ 472.

Ejemplo 21

Metil (3-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

El compuesto del título se preparó como se describe para Ejemplo 12 de metil (3- hidroxifenil)acetato y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3- dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 20-40% EtOAc en éter de petróleo 40-60°C como eluyente. El producto que contenía las fracciones se evaporó, y el residuo se disolvió en EtOAc, se lavó con K_2CO_3 acuoso

(2M) y se evaporó para producir el compuesto del título (0.097g, 66%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.55-7.48 (m, 2H), 7.46-7.40 (m, 3H), 7.26 (t, 1H), 6.90 (dd, 1H), 6.82-6.78 (m, 2H), 5.76 (t, 1H), 3.90 (t, 2H), 3.72 (s, 3H), 3.61 (s, 2H), 3.14-3.06 (m, 2H), 1.90-1.80 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 172.1, 159.8, 158.7, 135.7, 135.3, 131.8, 129.9, 129.8, 128.8, 125.3, 122.3, 115.5, 113.4, 107.2, 65.9, 61.7, 52.3, 42.4, 41.4, 29.0, 27.8; Espectro de Masa: $M+H^+$ 487.

Ejemplo 22

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-4-iloxi)propil]amino} isotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 4-hidroxipiridina y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4- metilbencenosulfonato con un tiempo de reacción de 15minutos. EtOAc se agregó a la mezcla de reacción, y la mezcla se lavó con agua, salmuera y se evaporó. El residuo se purificó dos veces por cromatografía en columna en gel de sílice (Horizons Biotage) usando 50-80% EtOAc en hexano, luego 50% EtOAc en DCM como eluyente para producir el compuesto del título (0.035g, 35%). ^{1}H NMR (500MHz $CDCl_3$): δ 8.44 (d, 2H), 7.54-7.48 (m, 2H), 7.48-7.41(m, 3H), 6.75 (d, 2H), 5.64 (t, 1H), 3.91 (t, 2H), 3.114-3.08 (m, 2H), 1.90-1.82 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 164.5, 159.8, 151.4, 135.2, 131.8, 129.9, 128.9, 125.2, 110.3, 107.6, 65.7, 61.8, 41.9, 28.8, 27.9; Espectro de Masa: $M+H^+$ 416.

Ejemplo 23

1,1-Dióxido de 4-(bencilamino)-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.150g, 0.500mmol) y bencilamina (0.110ml, 1.001mmol) en DMF (2ml) se calentó en el reactor microondas a 120°C durante 15 minutos. EtOAc se agregó, la mezcla se lavó con salmuera y se evaporó a sequedad. El residuo se purificó por cromatografía en columna de gel de sílice

(Horizons Biotage) usando 15-20% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.095g, 51%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 7.50-7.38 (m, 5H), 7.34-7.25 (m, 3H), 7.06-6.98 (m, 2H), 5.55 (bs, 1H), 4.02 (d, 2H), 1.77 (9H, s); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 136.8, 133.0, 131.9, 129.8, 129.0, 128.7, 128.2, 127.6, 124.8, 108.2, 61.6, 48.4, 27.9; Espectro de Masa $M+H^+$ 371.

Ejemplo 24

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.150g, 0.500mmol) y (2-feniletil)amina (0.121g, 1.001mmol) en MeCN (2ml) se calentó en un reactor microondas a 120°C durante 15 minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 15-20% EtOAc en éter de petróleo 40-60°C para producir el compuesto del título (0.124g, 65%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.51 (m, 2H), 7.51-7.45 (m, 3H), 7.30-7.18 (m, 3H), 6.87 (d, 2H), 5.35 (t, 1H), 3.14 (q, 2H), 2.62 (t, 2H), 1.73 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 137.6, 135.0, 131.8, 129.9, 128.9, 128.7, 127.0, 125.4, 107.5, 61.7, 45.1, 36.0, 27.8; Espectro de Masa $M-H^+$ 384.

Ejemplo 25

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[3-(feniltio)propil]amino}isotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 1,1-dióxido de 2-*terc*-butil-4-[(3-cloropropil)amino]-5-fenilisotiazol-3(2*H*)-ona y tiofenol a 100°C durante 45minutos. La mezcla de reacción se filtró, se evaporó a sequedad, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 10-20% EtOAc en hexano como eluyente para producir el compuesto del título (0.076g, 65%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.46-7.38 (m, 3H), 7.32-

7.18 (m, 5H), 5.32 (t, 1H), 3.02-2.96 (m, 2H), 2.70 (t, 2H), 1.74 (s, 9H), 1.68-1.60 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 135.6, 135.1, 131.8, 129.4, 129.9, 129.3, 128.9, 126.7, 125.1, 107.5, 61.8, 42.8, 31.0, 28.9, 27.9; Espectro de Masa: $M+H^+$ 431.

Ejemplo 26

1,1-Dióxido de 2-*terc*-butil-4-[(3-fenoxipropil)amino]-5-fenilisotiazol-3(2H)-ona

El compuesto del título se preparó como se describe para Ejemplo 24 de (3-fenoxipropil)amina y 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 17-20% EtOAc en hexano como eluyente para producir el compuesto del título (0.152g, 73%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.47 (m, 10 2H), 7.44-7.38 (m, 3H), 7.32-7.24 (m, 2H), 6.95 (t, 1H), 6.84 (d, 2H), 5.74 (t, 1H), 3.87 (t, 2H), 3.12-3.04 (m, 2H), 1.86-1.78 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 158.8, 135.3, 131.8, 129.7, 128.7, 125.3, 121.3, 114.6, 107.2, 65.9, 61.7, 42.5, 29.0, 27.8; Espectro de Masa $M+H^+$ 415.

Ejemplo 27

1,1-Dióxido de 2-*terc*-butil-4-{[3-(3-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 3-clorofenol y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 15 minutos. La mezcla de reacción se evaporó y se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 15% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.079g, 72%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.46-7.40 (m, 3H), 7.20 (t, 1H), 6.95 (d, 1H), 6.84 (s, 1H), 6.75 (dd, 1H), 5.67 (t, 1H), 3.86 (t, 1H), 3.11-3.04 (m, 2H), 1.86-1.80 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 159.3, 135.3, 135.1, 131.8, 130.5, 129.8, 128.8,

125.3, 121.5, 115.0, 113.2, 107.4, 66.2, 61.7, 42.4, 28.9, 27.8: Espectro de Masa $M+H^+$ 449.

Ejemplo 28

Metil 3-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoato

El compuesto del título se preparó como se describe para Ejemplo 12 de metil 3-hidroxibenzoato y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 15 minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando DCM como eluyente para producir el compuesto del título (0.077g, 54%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.66 (d, 1H), 7.54-7.48 (m, 3H), 4.47-7.42 (m, 3H), 7.36 (t, 1H), 7.07 (dd, 1H), 5.70 (t, 1H), 3.94-3.90 (m, 5H), 3.13-3.08 (m, 2H), 1.90-1.84 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 167.1, 159.8, 158.5, 135.3, 131.8, 131.7, 129.8, 129.7, 128.8, 125.3, 122.6, 120.2, 114.6, 107.3, 66.2, 61.7, 52.4, 42.3, 28.9, 27.8; Espectro de Masa $M+H^+$ 473.

Ejemplo 29

2-Bencil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona 1,1-dióxido

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona (Ejemplo 1) (0.150g, 0.36 mmol) se disolvió en TFA (3 ml) y se calentó en un reactor microondas a 120°C durante 20 minutos. La mezcla de reacción se concentró, y el residuo se disolvió repetidamente en DCM y se evaporó. El producto crudo se disolvió en MeCN seco (3 ml) y carbonato de potasio (0.251g, 1.82 mmol), y se agregó bromuro de bencilo (0.075g, 0.44 mmol). La mezcla de reacción se calentó a 120°C durante 15 minutos y luego a 130°C durante 5 minutos en un reactor microondas. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice usando una mezcla 90:10 de hexano y EtOAc como eluyente, para producir el compuesto del título (0.088 g, 54 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-

7.49 (m, 4H), 7.48-7.31 (m, 6H), 7.31-7.25 (m, 2H), 7.23-7.17 (m, 1H), 7.11-7.05 (m, 2H), 5.31-5.25 (m, 1H), 4.85 (s, 2H), 2.90-2.82 (m, 2H), 2.50-2.42 (m, 2H), 1.45-1.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 141.7, 135.6, 134.6, 131.8, 130.0, 129.0, 128.9, 128.9, 128.6, 128.5, 128.5, 126.2, 125.1, 107.0, 44.2, 43.8, 35.4, 29.2, 28.3 Espectro de Masa: $M-H^+$ 447.

Ejemplo 30

Ácido (4-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acético

El compuesto del título se preparó como se describe para Ejemplo 20 de metil (4-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetato (Ejemplo 32). La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 5% MeOH (+0.5% AcOH) en EtOAc como eluyente para producir el compuesto del título (0.05g, 8%). ^1H NMR (500MHz CD_3OD): δ 7.52-7.44 (m, 5H), 7.17 (d, 2H), 6.76 (d, 2H), 3.78 (t, 2H), 3.53 (s, 2H), 3.08 (t, 2H), 1.79-1.74 (m, 2H), 1.17 (s, 9H); Espectro de Masa: $M+H^+$ 473.

Ejemplo 31

1,1-Dióxido de 2-*terc*-butil-4-{[3-(3-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 12 de 3-fluorofenol y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 15 minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 15% EtOAc en hexano como eluyente para producir el compuesto del título (0.069g, 65%). ^1H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.46-7.42 (m, 3H), 7.26-7.20 (m, 1H), 6.70-6.60 (m, 2H), 6.59-6.55 (m, 1H), 5.69 (t, 1H), 3.86 (t, 1H), 3.12-3.07 (q, 2H), 1.90-1.82

(m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 164.8, 162.8, 159.9, 159.8, 135.3, 131.8, 130.5, 130.4, 129.8, 128.8, 125.3, 110.4, 108.2, 108.1, 107.3, 102.5, 102.3, 66.3, 61.7, 42.3, 28.9, 27.8; Espectro de Masa: $M+H^+$ 433.

Ejemplo 32

Metil (4-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

El compuesto del título se preparó como se describe para Ejemplo 12 de metil (4-hidroxifenil)acetato y 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato con un tiempo de reacción de 30 minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 25% EtOAc en hexano como eluyente para producir el compuesto del título (0.079g, 75%). ^1H NMR (500MHz $CDCl_3$): δ 7.52-7.44 (m, 2H), 7.14-7.38 (m, 3H), 7.17 (d, 2H), 6.78 (d, 2H), 5.72 (t, 1H), 3.85 (t, 2H), 3.68 (s, 3H), 3.56 (s, 2H), 3.10-3.00 (m, 2H), 1.84-1.78 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 172.5, 159.8, 157.7, 135.3, 131.8, 130.7, 130.5, 129.7, 128.8, 126.8, 125.3, 115.7, 114.7, 107.2, 66.1, 61.7, 52.2, 42.4, 40.5, 28.9, 27.8; Espectro de Masa: $M+H^+$ 487.

Ejemplo 33

1,1-Dióxido de 2-*terc*-butil-4-{[3-(4-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 5 de 1,1-dióxido de 2-*terc*-butil-4-[(3-bromopropil)amino]-5-fenilisotiazol-3(2*H*)-ona y 4-fluorofenol usando 3 equivalentes de K_2CO_3 y calentando a 80°C durante 15minutos, 100°C durante 1 hora y 120°C durante 1 hora. La mezcla de reacción se evaporó a sequedad, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 12-20% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.007g, 31%). ^1H NMR (500MHz $CDCl_3$): δ 7.54-

7.50 (m, 2H), 7.45-7.40 (m, 3H), 7.00-6.96 (m, 2H), 6.82-6.78 (m, 2H), 5.76 (t, 1H), 3.86 (t, 2H), 3.11-3.02 (m, 2H), 1.88-1.80 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 158, 154.7, 156.7, 135.3, 131.8, 129.7, 128.8, 125.3, 116.2, 160.0, 115.6, 115.5, 107.2, 66.7, 61.7, 42.5, 28.9, 27.8; Espectro de Masa: $M+H^+$ 433.

Ejemplo 34

1,1-Dióxido de 2-isopropil-5-fenil-4-({1-[4-(trifluorometil)pirimidin-2-il]piperidin-4-il}amino)isotiazol-3(2*H*)-ona

1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.200g, 0.70mmol), 1-(4-trifluorometil-pirimidin-2-il)-piperidin-4-ilamina (0.190g, 0.77mmol) y TEA (0.078g, 0.77mmol) se disolvió en MeCN seco (3ml) y se calentó en un reactor microondas a 120°C durante 30 minutos. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice usando una mezcla 65:35 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.280g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45-8.41 (m, 1H), 7.58-7.52 (m, 2H), 7.49-7.42 (m, 3H), 6.74-6.70 (m, 1H), 5.26-5.19 (m, 1H), 4.59-4.51 (m, 2H), 4.41 (hep, 1H), 3.26-3.16 (m, 1H), 2.58-2.49 (m, 2H), 1.78-1.71 (m, 2H), 1.57 (d, 6H), 1.35-1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 160.3, 158.7, 156.6, 156.3, 134.5, 131.9, 130.2, 129.0, 125.3, 121.8, 119.6, 107.2, 104.9, 50.7, 47.9, 42.4, 32.2, 20.4; Espectro de Masa: $M-H^+$ 496.

Ejemplo 35

3-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propil 4-hidroxibenzoato

El compuesto del título se preparó como se describe para Ejemplo 5 de 1,1-dióxido 2-*terc*-butil-4-[(3-bromopropil)amino]-5-fenilisotiazol-3(2*H*)-ona y ácido 4-hidroxibenzoico con un tiempo de reacción de 1.5 horas. La mezcla de reacción se acidificó con HCl (1N) t se extrajo con EtOAc. Las capas orgánicas se combinaron y se evaporaron a sequedad. El residuo se trituró en MeOH, el disolvente se decantó, y el residuo se purificó por

cromatografía en columna de gel de sílice (Horizons Biotage) usando 50% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.028g, 21%). ^{1}H NMR (500MHz CD_3CN): δ 7.80 (d, 2H), 7.62 (bs, 1H), 7.56-7.48 (m, 2H), 7.56-7.42 (m, 3H), 5.93 (t, 1H), 4.09 (t, 2H), 3.08-3.03 (m, 2H), 1.76-1.68 (m, 11H); ^{13}C NMR (125MHz CD_3CN): δ 166.5, 160.6, 159.8, 135.2, 132.2, 131.8, 129.9, 128.9, 125.0, 122.2, 115.5, 107.4, 62.2, 61.1, 41.1, 28.4, 27.1; Espectro de Masa: $M+H^+$ 459.

Ejemplo 36

1,1-Dióxido de 4-(bencilamino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.200g, 0.70mmol), bencilamina (0.082g, 0.77mmol) y TEA (0.078g, 0.77mmol) se disolvió en MeCN (3 ml) y se calentó en un reactor microondas a 120°C durante 5 minutos. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice usando una mezcla 75:25 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.145g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.36 (m, 5H), 7.32-7.26 (m, 3H), 7.05-7.00 (m, 2H), 5.60-5.51 (m, 1H), 4.43 (hep, 1H), 4.08-4.02 (m, 2H), 1.61 (d, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 136.5, 135.2, 131.7, 129.8, 129.0, 128.7, 128.1, 127.5, 124.8, 107.9, 48.3, 47.8, 20.3; Espectro de Masa: $M-H^+$ 357.

Ejemplo 37

1,1-Dióxido de 2-[2-(3-fluorofenil)etil]-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona (Ejemplo 1) (0.150g, 0.36mmol) se disolvió en TFA (3 ml) y se calentó en un reactor microondas a 120°C durante 20 minutos. El disolvente se evaporó, y el producto crudo se re-evaporó de DCM (2x5 ml). El producto crudo, carbonato de potasio (0.251g, 1.82mmol) y bromuro de 3-fluorofenetilo (0.221g, 1.09mmol) se disolvió en MeCN seco (3 ml) y se

calentó en un reactor microondas a 140°C durante 10 minutos. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice usando una mezcla 85:15 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.113g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.41 (m, 5H), 7.34-7.25 (m, 3H), 7.23-7.17 (m, 1H), 7.14-7.01 (m, 4H), 7.00-6.93 (m, 1H), 5.28-5.19 (m, 1H), 3.98-3.90 (m, 2H), 3.18-3.10 (m, 2H), 2.91-2.83 (m, 2H), 2.50-2.43 (m, 2H), 1.44-1.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 162.2, 159.1, 141.7, 140.3, 140.2, 135.6, 131.8, 130.4, 130.3, 130.0, 128.9, 128.6, 128.5, 126.2, 125.0, 124.8, 116.2, 116.0, 114.1, 113.9, 107.0, 44.2, 41.1, 35.4, 34.4, 29.2, 28.3; Espectro de Masa: M-H^+ 479.

Ejemplo 38

1,1-Dióxido de 4-[(cis-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se aisló por separación de la mezcla de cis y trans isómeros de 1,1-dióxido de 4-[(4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (50:50, 130mg) por HPLC (C8, 0.05M NH4OAc (pH=4.1):MeCN 1:1), produciendo el compuesto del título (52mg). ^{1}H NMR (500 MHz, $CDCl_3$): 67.53-7.48 (m, 2H), 7.45-7.41 (m, 3H), 5.32-5.24 (m, 1H), 4.40 (hep, 1H), 3.78-3.71 (m, 1H), 3.05-2.94 (m, 1H), 1.62-1.40 (m, 6H), 1.58 (d, 6H), 1.32-1.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 134.5, 131.9, 129.9, 128.9, 125.5, 106.3, 65.7, 50.5, 47.8, 31.1, 27.4, 20.4; Espectro de Masa: M-H^+ 365.

Ejemplo 39

1,1-Dióxido de 2-*terc*-butil-4-[(4-fenoxibutil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 24 de 1 equivalente de (4-fenoxibutil)amina, 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1 equivalente de TEA a 100°C. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage)

usando 10-20% EtOAc en hexano como eluyente, lo cual produjo el compuesto del título (0.172g, 80%) como un sólido. ^{1}HNMR (500MHz $CDCl_3$): ^{1}HNMR (500MHz $CDCl_3$): δ 7.54-7.50(m, 2H), 7.44-7.38 (m, 3H), 7.32-7.25 (m, 2H), 6.96 (t, 1H), 6.83 (d, 2H), 5.34 (t, 1H), 3.81 (t, 2H), 2.98-2.90 (m, 2H), 1.75 (s, 9H), 1.64-1.53 (m, 4H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 158.9, 135.2, 131.8, 129.8, 129.7, 128.8, 125.3, 121.0, 114.6, 107.2, 67.1, 61.7, 43.9, 27.9, 26.6, 26.4; Espectro de Masa: $M+H^+$ 429.

Ejemplo 40

1,1-Dióxido de 2-*terc*-butil-4-({3-[(1-oxidopiridin-3-il)oxi]propil} amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-3-iloxi)propil]amino} isotiazol-3(2*H*)-ona (Ejemplo 5) (0.202g, 0.49mmol) se disolvió en DCM seco (15 ml) y se enfrió a 0°C con un baño helado. *m*CPBA (70%) (0.120g, 0.53mmol) se agregó, y se retiró el baño helado, y la mezcla de reacción se dejó alcanzar la temperatura de la sala. Luego de agitar durante 2 horas, la mezcla de reacción se extrajo con solución de $NaHCO_3$ acuoso saturado (20 ml) y salmuera (20 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se evaporó. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 10:90 de heptano y EtOAc y luego DCMrMeOH 97:3 como eluyente, para producir el compuesto del título (0.160 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90-7.83 (m, 2H), 7.51-7.37 (m, 5H), 7.16-7.09 (m, 1H), 6.80-6.74 (m, 1H), 5.68-5.57 (m, 1H), 3.85-3.76 (m, 2H), 3.09-3.02 (m, 2H), 1.85-1.76 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 157.0, 135.1, 133.0, 131.8, 129.9, 128.9, 128.2, 125.7, 125.2, 113.5, 107.6, 67.0, 61.8, 60.6, 41.7, 32.1, 28.8, 27.8, 22.9; Espectro de Masa: $M-H^+$ 432.

Ejemplo 41

1,1-Dióxido de 2-*terc*-butil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 24 de (2-fenoxietil)amina y 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 15-20% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.026g, 13%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.60-7.51 (m, 2H), 4.72-7.42 (m, 2H), 7.29 (t, 2H), 6.99 (t, 1H), 6.84 (d, 2H), 5.67 (t, 1H), 3.89 (t, 2H), 3.25 (q, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.7, 158.3, 135.2, 131.7, 129.5, 129.8, 129.0, 125.2, 121.7, 114.7, 108.1, 65.9, 61.8, 43.5, 27.8.; Espectro de Masa $M+H^+$

Ejemplo 42

1,1-Dióxido de 4-(bencilamino)-2-ciclopentil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido 4-(bencilamino)-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona (Ejemplo 23) y bromociclopentano en una manera similar a la descrita para Ejemplo 2 y 3. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.48-7.36 (m, 5H), 7.31-7.26 (m, 3H), 7.04-6.99 (m, 2H), 5.61-5.53 (m, 1H), 4.39 (p, 1H), 4.05 (d, 2H), 2.27-2.10 (m, 4H), 1.97-1.87 (m, 2H), 1.7-1.6 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$):δ 158.8, 136.5, 135.2, 131.7, 129.8, 128.9, 128.7, 128.1, 127.4, 124.9, 107.9, 55.2, 48.3, 29.4, 24.1; Espectro de Masa: $M-H^+$383.

Ejemplo 43

1,1-Dióxido de 2-*terc*-butil-4-{[3-(4-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-[(3-bromopropil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona y 4-metoxifenol en una manera similar a la descrita para Ejemplo 5 y 33 y 35. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.46-7.42 (m, 3H), 6.86-

6.78 (m, 4H), 5.79 (t, 1H), 3.85 (t, 2H), 3.79 (s, 3H), 3.12-3.04 (m, 2H), 1.85-1.80 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 154.3, 152.7, 135.4, 131.8, 129.7, 128.8, 125.4, 115.5, 114.9, 107.1, 66.8, 61.7, 55.9, 42.6, 29.1, 27.9.; Espectro de Masa: $M+H^+$ 445.

Ejemplo 44

1,1-Dióxido de 4-[(4,4-difluorociclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.155g, 0.54mmol), 4,4-difluorociclohexilamina (0.11g, 0.81mmol) y TEA (0.082g, 0.81mmol) se disolvió en MeCN seco (3 ml) y se calentó en un reactor microondas a 130°C durante 10 minutos. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice usando una mezcla 85:15 de hexano y EtOAc como eluyente, para producir el compuesto del título (0.142g, 68%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.49-7.42 (m, 3H), 5.23-5.16 (m, 1H), 4.41 (hep, 1H), 3.10-3.00 (m, 1H), 1.97-1.86 (m, 2H), 1.77-1.68 (m, 2H), 1.57 (d, 6H), 1.49-1.37 (m, 2H), 1.37-1.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 134.5, 131.8, 130.3, 129.0, 125.1, 123.9, 122.0, 120.0, 107.3, 49.9, 47.9, 32.1, 31.9, 31.7, 29.0, 28.9, 20.4; Espectro de Masa: $M-H^+$ 385.

Ejemplo 45

1,1-Dióxido de 4-(bencilamino)-2-butil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y bencilamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (CD_3CN) δ 7.47-7.42 (m, 1H), 7.40-7.35 (m, 2H), 7.34-7.29 (m, 2H), 7.23-7.18 (m, 3H), 6.88-6.83 (m, 2H), 6.44-6.35 (m, 1H), 4.16 (d, J=6.6Hz, 2H), 3.68 (t, J=7.3Hz, 2H), 1.82-1.71 (m, 2H), 1.49-1.38 (m, 2H), 0.98 (t, J=7.4Hz, 3H); Espectro de Masa: $M+H^+$ 371.

Ejemplo 46

1,1-Dióxido de 2-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 2-feniletanamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}HNMR (500MHz $CDCl_3$): δ 7.58-7.52 (m, 2H), 7.50-7.42 (m, 2H), 7.30-7.20 (m, 4H), 6.88 (dd, 2H), 5.38 (t, 1H), 3.70 (t, 2H), 3.18 (dt, 2H), 2.62 (t, 2H), 1.88-1.78 (m, 2H), 1.50-1.40 (m, 2H), 0.98 (t, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.4, 137.8, 137.5, 131.8, 130.0, 129.0, 128.9, 128.7, 127.1, 125.2, 107.2, 45.1, 40.4, 36.0, 30.4, 20.3, 13.8; Espectro de Masa $M+H^+$ 385.5

Ejemplo 47

1,1-Dióxido de 2-butil-4-{[4-(difluorometoxi)bencil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1-[4-(difluorometoxi)fenil]metanamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (CD_3CN) δ 1.46-7.4l (m, 1H), 7.39-7.33 (m, 2H), 7.29-7.25 (m, 2H), 6.98-6.93 (m, 2H), 6.86-6.81 (m, 2H), 6.72 (t, *J*=74.4Hz, 1H), 6.48-6.39 (m, 1H), 4.16 (d, *J*=6.6Hz, 2H), 3.67 (t, *J*=7.2Hz, 2H), 1.81-1.72 (m, 2H), 1.49-1.38 (m, 2H), 0.98 (t, *J*=7.3Hz, 3H); Espectro de Masa: $M+H^+$ 437.

Ejemplo 48

1,1-Dióxido de 4-[(trans-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se aisló por separación de una mezcla de los cis y trans isómeros de 1,1-dióxido de 4-[(4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (50:50, 130mg) por HPLC (C8, 0.05M NH4OAc (pH=4.1):MeCN 1:1), lo cual produjo el compuesto del título (73mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.46-7.42 (m, 3H), 5.16-5.08 (m, 1H), 4.39 (hep, 1H), 3.52-3.42 (m, 1H), 2.96-2.85 (m, 1H), 1.82-1.70 (m, 4H), 1.57 (d, 6H), 1.16-1.06 (m, 2H), 0.88-0.77 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 134.7, 131.8, 130.1, 128.9, 125.2, 106.5, 69.4, 51.3, 47.8, 33.5, 31.0, 20.4; Espectro de Masa: M-H$^+$ 365.

Ejemplo 49

1,1-Dióxido de 2-*terc*-butil-4-[(3-hidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.300g, 1.001mmol), 3-hidroxipropilamina (0.08ml, 1.001mmol) y TEA (0.14ml, 1.001mmol) en MeCN (5ml) se agitó a temperatura de la sala. Luego de 18 horas, la mezcla se evaporó a sequedad, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) eluyendo con 33-80% EtOAc (+0.5% TEA) en éter de petróleo 40-60°C para producir el compuesto del título (0.145g, 43%). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.46-7.42 (m, 3H), 5.77 (t, 1H), 3.62 (q, 2H), 3.01 (q, 2H), 1.74 (s, 9H), 1.63 (qt, 2H); Espectro de Masa: M-H$^+$ 337.

Ejemplo 50

1,1-Dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-3-ilmetil)isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona (Ejemplo 1) y 3-(bromometil)piridina en una manera similar a la descrita para Ejemplo 2 y 3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80-8.76 (m, 1H), 8.62-8.58 (m, 1H), 7.89-7.85 (m, 1H), 7.53-7.41 (m, 5H), 7.34-7.24 (m, 3H), 7.22-7.17 (m, 1H), 7.09-7.04 (m, 2H), 5.31-5.25 (m, 1H), 4.84 (s, 2H), 2.90-2.83 (m, 2H), 2.49-2.42 (m, 2H), 1.44-1.35 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.1, 150.3, 149.8, 141.6, 136.7, 135.5, 131.7, 130.3, 130.0, 128.8, 128.5, 128.4, 126.1, 124.7, 123.7, 107.0, 44.1, 41.1, 35.3, 29.0, 28.2; Espectro de Masa: M-H$^+$ 448.

Ejemplo 51

1,1-Dióxido de 2-butil-4-[(4-hidroxiciclohexil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 4-aminociclohexanol en una manera similar a la descrita para Ejemplo 6 y 7, lo cual proporcionó una mezcla de cis y trans isómeros. ^{1}H NMR (500MHz, CD_3CN): δ 0.61-0.72 (m, 2H), 0.95-0.99 (m, 6H), 1.02-1.10 (m, 2H), 1.17-1.27 (m, 2H), 1.38-1.60 (m, 12H), 1.64-1.80 (m, 8H), 2.46 (d, 1H), 2.55 (d, 1H), 2.86-3.05 (m, 2H), 3.29-3.38 (m, 1H), 3.60-3.69 (m, 5H), 5.55-5.66 (m, 2H), 7.47-7.57 (m, 10H).

Ejemplo 52

Ácido 4-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoico

Metil 4-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoato (0.90g, 0.19mmol) y LiI (0.382g, 2.86mmol) se disolvieron en piridina seca (1mL) y se calentaron a reflujo durante 4 horas y luego se dejaron a temperatura de la sala de un día para otro. La mezcla de reacción se purificó por cromatografía rápida usando primero hexano y EtOAc y luego EtOAc y MeOH como eluyente, lo cual produjo el compuesto del título (0.003g, 3.4%). ^{1}HNMR(CD3CN): 7.98 (d, 2H), 7.56-7.48 (m, 5H), 6.90 (d, 2H), 6.02 (t, 1H), 3.90 (t, 2H), 3.12-3.08 (m, 2H), 1.82-1.76 (t, 2H), 1.17 (s, 9H); Espectro de Masa: $M+H^+$ 459.

Ejemplo 53

1,1-Dióxido de 2-*terc*-butil-4-{[3-(4-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-[(3-bromopropil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona y 4-clorofenol en una manera similar a la descrita para Ejemplo 5. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.48 (m, 2H), 7.46-7.40 (m, 3H), 7.26-7.20 (m, 2H), 6.82-6.76 (m, 2H), 5.72 (t, 1H), 3.86 (t, 2H), 3.11-3.06 (m, 2H), 1.88-1.80 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 157.1, 135.3, 131.8, 129.8, 129.6, 128.8, 126.2, 125.3, 115.9, 107.3, 66.4, 61.7, 42.4, 28.9, 27.8.; Espectro de Masa: $M+H^+$ 449.

Ejemplo 54

1,1-Dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-4-ilmetil)isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona (Ejemplo 1) y 4-(clorometil)piridina en una manera similar a la descrita para Ejemplo 2 y 3. ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.66-8.60 (m, 2H), 7.54-7.38 (m, 7H), 7.31-7.24 (m, 2H), 7.23-7.16 (m, 1H), 7.10-7.04 (m, 2H), 5.34-5.27 (m, 1H), 4.82 (s, 2H), 2.92-2.84 (m, 2H), 2.50-2.42 (m, 2H), 1.45-1.35 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.3, 150.3, 143.4, 141.5, 135.4, 131.7, 130.0, 128.8, 128.5, 128.4, 126.1, 124.7, 123.1, 107.2, 44.1, 42.3, 35.3, 31.5, 29.0, 28.2; Espectro de Masa: M-H$^+$ 448.

Ejemplo 55

1,1-Dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-butil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1-(1,3-benzodioxol-5-il)metanamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (500MHz, CD_3CN): δ 0.97 (t, 3H), 1.39-1.48 (m, 2H), 1.72-1.80 (m, 2H), 3.67 (t, 2H), 4.05 (d, 2H), 5.91 (s, 2H), 6.26-6.34 (m, 2H), 6.64 (d, 1H), 7.32-7.48 (m, 5H).

Ejemplo 56

1,1-Dióxido de 4-(2,3-dihidro-1H-inden-2-ilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona e indan-2-amina en una manera similar a la descrita para Ejemplo 1. ^{1}H NMR (400 MHz, CD_3CN): 67.65-7.60 (m, 2H), 7.55-7.50 (m, 3H), 7.13-7.11 (m, 4H), 5.90 (d, 1H), 4.06-3.98 (m, 1H), 3.83 (t, 2H), 3.67 (t, 2H), 3.38 (s, 3H), 2.84-2.81 (m, 4H); Espectro de Masa: M+H$^+$ 399.

Ejemplo 57

1,1-Dióxido de 2-butil-4-[(2-morfolin-4-iletil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 2-morfolin-4-iletanamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.50 (m, 2H), 7.50-7.00 (m, 3H), 6.05 (t, 1H), 3.78-3.65 (m, 6H), 2.92-2.88 (m, 2H), 2.46-2.32 (m, 6H), 1.88-1.80 (m, 2H), 1.50-1.42 (m, 2H), 1.00 (t, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.2, 135.9, 131.6, 129.8, 128.9, 125.3, 107.2, 67.1, 56.4, 53.2, 40.3, 40.2, 30.5, 20.3, 13.8.; Espectro de Masa: $M+H^+$ 394.

Ejemplo 58

1,1-Dióxido de 2-*terc*-butil-4-{[3-(4-isopropilfenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato y 4-isopropilfenol en una manera similar a la descrita para Ejemplo 12. ^{1}H NMR (500MHz $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.48-7.42 (m, 3H), 7.16 (d, 2H), 6.80 (d, 2H), 5.78 (t, 1H), 3.88 (t, 2H), 3.10-3.05 (m, 2H), 2.92- 2.82 (m, 1H), 1.85-1.80 (m, 2H), 1.75 (s, 9H), 1.24 (d, 6H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 156.6, 141.8, 135.4, 131.8, 129.7, 128.8, 127.5, 125.4, 114.4, 107.1, 66.1, 61.7, 42.6, 33.5, 29.0, 27.9, 24.4; Espectro de Masa: $M+H^+$ 457.

Ejemplo 59

1,1-Dióxido de 4-({3-[bencil(butil)amino]propil}amino)-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-[(3-bromopropil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona y N-bencilbutan-1-amina en una manera similar a la descrita para Ejemplo 5. ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.44 (m, 2H), 7.42-7.38 (m, 3H), 7.33-7.30

(m, 2H), 7.30-7.24 (m, 3H), 6.36 (t, 1H), 3.48 (s, 2H), 2.86-2.78 (m, 2H), 2.40-2.12 (m, 4H), 1.76 (s, 9H), 1.56-1.44 (m, 4H), 1.36-1.24(m, 2H), 0.91(t, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.8, 139.4, 135.6, 131.8, 129.4, 129.2, 128.9, 128.4, 127.2, 125.7, 106.3, 61.5, 59.2, 54.1, 52.0, 44.3, 29.2, 27.8, 26.3, 20.9, 14.3; Espectro de Masa: M+H$^+$ 484.

Ejemplo 60

1,1-Dióxido de 2-*terc*-butil-4-{[3-(3,5-dipropoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-[(3-bromopropil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona y 3,5-dipropoxifenol en una manera similar a la descrita para Ejemplo 5. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.46-7.41 (m, 3H), 6.12-6.09 (m, 1H), 6.08-6.06 (m, 2H), 5.89-5.83 (m, 1H), 3.93-3.84 (m, 6H), 3.09-3.03 (m, 2H), 1.87-1.76 (m, 6H), 1.74 (s, 9H), 1.07-1.01 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 160.2, 159.9, 135.4, 131.8, 129.7, 128.8, 125.3, 107.1, 94.8, 94.6, 94.4, 94.0, 69.8, 66.4, 61.6, 42.7, 28.8, 27.8, 22.8, 10.8; Espectro de Masa: M+H$^+$ 531.

Ejemplo 61

1,1-Dióxido de 2-*terc*-butil-4-[(2,2-difeniletil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 2,2-difeniletanamina en una manera similar a la descrita para Ejemplo 1. ^{1}H NMR (500MHz $CDCl_3$): δ 7.59-7.54(m, 2H), 7.48-7.43 (m, 3H), 7.27 (t, 4H), 7.22 (t, 2H), 6.97 (d, 4H), 5.25 (t, 1H), 3.96 (t, 1H), 3.50 (dd, 2H), 1.70 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.6, 140.8, 135.0, 131.7, 129.9, 129.0, 128.0, 127.3, 125.3, 108.1, 61.7, 50.7, 48.3, 27.8; Espectro de Masa: M+H$^+$ 461.

Ejemplo 62

1,1-Dióxido de 2-etil-4-{[2-(1H-imidazol-4-il)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-etil-5-fenilisotiazol-3(2*H*)-ona y 2-(1H-imidazol-4-il)etanamina en una manera similar a la descrita para Ejemplo 1. ^{1}H NMR (500 MHz, CD_3OD): δ 7.54-7.42 (m, 6H), 6.51-6.48 (m, 1H), 3.71 (q, 2H), 3.14 (t, 2H), 2.55 (t, 2H), 1.36 (t, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 159.9, 137.3, 136.1, 132.9, 132.3, 130.6, 129.7, 126.9, 117.2, 107.2, 44.6, 36.0, 27.8, 14.0; Espectro de Masa: $M+H^+$ 347.

Ejemplo 63

1,1-Dióxido de 2-butil-4-[(4-morfolin-4-ilbencil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1-(4-morfolin-4-ilfenil)metanamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.46-7.40 (m, 3H), 6.94 (d, 2H), 6.81 (d, 2H), 5.47 (t, 1H), 3.95 (d, 2H), 3.87 (t, 4H), 3.72 (t, 2H), 3.15 (t, 4H), 1.88- 1.80 (m, 2H), 1.52-1.42 (m, 2H), 0.99 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 151.3, 135.8, 131.8, 129.9, 128.9, 128.8, 127.6, 125.1, 115.9, 108.0, 67.0, 49.4, 48.1, 40.4, 30.5, 20.3, 13.8; Espectro de Masa: $M+H^+$456.

Ejemplo 64

1,1-Dióxido de 2-butil-4-{[3-(2-metoxietoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 3-(2-metoxietoxi)propan-1-amina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.50 (m, 2H), 7.48-7.42 (m, 3H), 6.04 (t, 1H), 3.70 (t, 2H), 3.58 (s, 4H), 3.46 (t, 2H), 3.40 (s, 3H), 3.04-2.98 (m, 2H), 1.88-1.80 (m, 2H), 1.70-1.66 (m, 2H), 1.50-1.40 (m, 2H), 0.98 (t, 3H); ^{13}C NMR (125MHz $CDCl_3$):

δ 159.2, 135.9, 131.8, 129.7, 128.8, 125.4, 106.4, 72.1, 70.7, 69.9, 59.3, 43.3, 40.2, 30.5, 28.9, 20.3, 13.8; Espectro de Masa: $M+H^+$ 397.

Ejemplo 65

1,1-Dióxido de 2-butil-4-[(3-morfolin-4-ilpropil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 3-morfolin-4-ilpropan-1-amina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.58 (bs, 1H), 7.58-7.52 (m, 2H), 7.48-7.40 (m, 3H), 3.84-3.78 (m, 4H), 3.70 (t, 2H), 2.98-2.92 (m, 2H), 2.50-2.38 (m, 6H), 1.86-1.80 (m, 2H), 1.62-1.52 (m, 2H), 1.50-1.40 (m, 2H), 0.98 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 136.4, 131.8, 129.5, 128.7, 125.7, 105.9, 66.9, 58.3, 54.0, 45.6, 40.2, 30.5, 24.1, 20.3, 13.8; Espectro de Masa: $M+H^+$ 408.

Ejemplo 66

1,1-Dióxido de 2-butil-4-[(2-metoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 2-metoxietanamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (400 MHz, CD_3CN): δ 7.55-7.49 (m, 5H), 5.83 (bs, 1H), 3.67 (t, 2H), 3.27 (t, 2H), 3.21 (s, 3H), 3.05-3.00 (m, 2H), 1.80-1.72 (m, 2H), 1.48-1.38 (m, 2H), 0.97 (t, 3H); Espectro de Masa: $M+H^+$ 339.

Ejemplo 67

1,1-Dióxido de 2-(2-metoxietil)-5-fenil-4-(tetrahidro-2H-piran-4-ilamino) isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona y tetrahidro-2H-piran-4-amina en una manera similar a la descrita para Ejemplo 1. ^{1}H NMR (400 MHz, CD_3CN): δ 7.58-7.50 (m, 5H), 5.70 (d, 1H), 3.84 (t, 2H), 3.74-3.66 (m, 4H),

3.35 (s, 3H), 3.21-3.10 (m, 1H), 2.86-2.78 (m, 2H), 1.61-1.54 (m, 2H), 1.48-1.36 (m, 2H); Espectro de Masa: $M+H^+$ 367.

Ejemplo 68

1,1-Dióxido de 4-(hexilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido 4-cloro-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona y hexan-1-amina en una manera similar a la descrita para Ejemplo 1. ^{1}H NMR (400 MHz, CD_3CN): δ 7.48-7.56 (m, 5H), 5.83-5.99 (m, 1H), 3.83 (t, 2H), 3.67 (t, 2H), 3.35 (s, 3H), 2.84-2.90 (m, 2H), 1.13-1.32 (m, 4H), 0.92-1.09 (m, 4H), 0.82 (t, 3H); Espectro de Masa: $M-H^+$ 365.

Ejemplo 69

1,1-Dióxido de 4-[(4-hidroxiciclohexil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona y 4-aminociclohexanol en una manera similar a la descrita para Ejemplo 1. ^{1}H-NMR(CD_3CN): δ 7.58-7.48 (m, 5H), 5.66 (d, *J*=8.5Hz, 1H), 3.83 (t, *J* =5.7Hz, 2H), 3.67 (t, *J* =5.7Hz, 2H), 3.65-3.60 (m, 1H), 3.35 (s, 3H), 3.06-2.95 (m, 1H), 2.49 (d, *J*= 3.5Hz, 1H), 1.62-1.35 (m, 6H), 1.11-0.99 (m, 2H); MS (ESI+) 381.06 ($M + 1H^+$).

Ejemplo 70

1,1-Dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona y 1-(1,3-benzodioxol-5-il)metanamina en una manera similar a la descrita para Ejemplo 1. ^{1}H NMR (400 MHz, CD_3CN): δ 7.32-7.49 (m, 5H), 6.64 (d, 1H), 6.31-6.38 (m, 2H), 6.25-6.29 (m, 1H), 5.91 (s, 2H), 4.05 (d, 2H), 3.83 (t, 2H), 3.67 (t, 2H), 3.35 (s, 3H); Espectro de Masa: $M-H^+$ 415.

Ejemplo 71

1,1-Dióxido de 2-butil-4-[(4-metoxibencil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de1,1-dióxido de 2-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1-(4-metoxifenil)metanamina en una manera similar a la descrita para Ejemplo 6 y 7. ^{1}H NMR (CD_3CN) δ 7.50-7.33 (m, 5H), 6.79-6.74 (m, 4H), 6.34-6.26 (m, 1H), 4.08 (d, *J*=6.7Hz, 2H), 3.75 (s, 3H), 3.67 (t, *J*=7.2Hz, 2H), 1.81-1.71 (m, 2H), 1.49-1.38 (m, 2H), 0.97 (t, *J* =7.5 Hz, 3H); Espectro de Masa: M-H$^+$ 399.

Ejemplo 72

1,1-Dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-2-ilmetil)isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona (Ejemplo 1) y 2-(bromometil)piridina en una manera similar a la descrita para Ejemplo 2 y 3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65-8.60 (m, 1H), 7.74-7.67 (m, 1H), 7.56-7.51 (m, 2H), 7.50-7.41 (m, 4H), 7.31-7.17 (m, 4H), 7.10-7.05 (m, 2H), 5.35-5.28 (m, 1H), 5.01 (s, 2H), 2.94-2.84 (m, 2H), 2.50-2.42 (m, 2H), 1.45-1.35 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.4, 154.4, 149.7, 141.6, 137.1, 135.5, 131.7, 129.9, 128.8, 128.5, 128.4, 126.1, 124.9, 123.0, 121.9, 107.2, 44.9, 44.1, 35.3, 29.1, 28.2; Espectro de Masa: M-H$^+$ 448.

Ejemplo 73

1,1-Dióxido de 2-*terc*-butil-4-{[3-(3-hidroxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

Una mezcla de 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato (0.045g, 0.091mmol), resorcinol (0.02Og, 0.183mmol) y K_2CO_3 (0.063g, 0.457mmol) en MeCN (2ml) se calentó en un reactor microondas a 120°C durante 10minutos. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage)

usando 0-50% EtOAc en DCM como eluyente para producir el compuesto del título (0.016g, 41%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.48 (m, 2H), 7.46-7.41 (m, 3H), 7.13 (t, 1H), 6.46-6.41 (m, 2H), 6.39-6.36 (m, 1H), 5.75 (t, 1H), 5.14 (s, 1H), 3.86 (t, 2H), 3.11-3.04 (m, 2H), 1.86-1.78 (m, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): 159.9, 157.1, 135.4, 131.8, 130.4, 129.8, 128.8, 125.3, 108.5, 107.1, 106.9, 102.3, 66.1, 61.8, 42.5, 28.9, 27.8; Espectro de Masa: $M+H^+$ 431.

Ejemplo 74

Ácido 3-{3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}benzoico

El compuesto del título se preparó de 3-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propil 4-metilbencenosulfonato y ácido 3-hidroxibenzoico en una manera similar a la descrita para Ejemplo 12.

^{1}H NMR (500 MHz, *d8*-THF): δ 7.62-7.58 (d, 1H), 7.57-7.51 (m, 2H), 7.49 (s, 1H), 7.46-7.42 (m, 3H), 7.31 (t, 1H), 7.30 (t, 1H), 6.51 (t, 1H), 3.82 (t, 2H), 3.14-3.08 (m, 2H), 1.83-1.78 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, *d8*-THF): δ 166.7, 159.8, 158.9, 135.5, 132.5, 131.9, 129.2, 129.1, 128.4, 126.4, 122.1, 119.1, 114.9, 106.9, 65.6, 60.4, 41.3, 29.0, 26.9; Espectro de Masa: $M+H^+$ 459.

Ejemplo 75

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona

TFA (1ml) se agregó a una solución de *terc*-butil 4-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-carboxilato (Ejemplo 86) (2.138g, 4.612mmol) en DCM (20ml), y la mezcla se agitó a temperatura de la sala durante 80 minutos. TFA (1ml) se agregó, y la mezcla de reacción se agitó durante 18 horas. La mezcla de reacción se basificó por la adición de $NaHCO_3$ acuoso saturado. La capa orgánica se separó, y la fase acuosa se extrajo con DCM. Las fases orgánicas

combinadas se lavaron con salmuera, y se evaporaron para producir el compuesto del título (1.630g, 97%) como un sólido. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.40 (m, 3H), 5.20 (d, 1H), 3.08-2.92 (m, 3H), 2.19 (dt, 2H), 1.74 (s, 9H), 1.72-1.46 (m, 2H), 1.36-1.24 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.9, 134.0, 131.8, 130.1, 128.9, 125.3, 107.1, 61.8, 50.2, 44.7, 33.1, 27.9; Espectro de Masa: $M+H^+$ 364.

Ejemplo 76

1,1-Dióxido de 2-*terc*-butil-4-[(2-hidroxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 49 de 2-aminoetanol y 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando DCM como eluyente para producir el compuesto del título (1.788g, 55%) como un aceite. ^{1}H NMR (500MHz,): δ 7.50-7.44 (m, 5H), 6.81 (t, 1H), 4.69 (t, 1H), 3.29-3.22 (m, 2H), 3.86-2.80 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (125MHz DMSO-d_6): 159.9, 136.1, 132.1, 130.0, 129.2, 125.9, 105.4, 61.2, 59.5, 46.6, 27.8; Espectro de Masa: $M+H^+$ 325.

Ejemplo 77

4-{2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenil metanosulfonato

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol) y 4-(2-aminoetil)fenil metanosulfonato (0.149g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.140g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H), 7.48-7.43 (m, 3H), 7.14-7.10 (m, 2H), 6.83-6.78 (m, 2H), 5.43-5.36 (m, 1H), 3.15-3.08 (m, 2H), 2.61-2.55 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 148.2, 137.1, 134.9, 131.9, 130.3, 130.0, 129.0,

125.3, 122.4, 107.7, 61.8, 44.9, 37.6, 35.5, 27.8; Espectro de Masa: M-H$^+$ 479.

Ejemplo 78

4-{2-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}bencenosulfonamida

1,1-Dóxido de 2-*terc*-Butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), 4-(2-aminoetil)bencenosulfonamida (0.139g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.122g, 45%). ^{1}H NMR (500 MHz, *d8*-THF): δ 7.70-7.65 (m, 2H), 7.58-7.52 (m, 2H), 7.51-7.45 (m, 3H), 6.90-6.84 (m, 2H), 6.53-6.47 (m, 1H), 6.38-6.34 (m, 1H), 3.19-3.12 (m, 2H), 2.64-2.58 (m, 1H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, *d8*-THF): δ 159.7, 143.3, 142.4, 135.2, 132.0, 129.4, 128.8, 128.6, 126.4, 126.3, 107.2, 60.6, 44.7, 35.6, 27.0; Espectro de Masa: M-H$^+$ 464.

Ejemplo 79

1,1-Dióxido de 2-*terc*-butil-4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il}amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-Butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (200mg, 0.667mmol) se disolvió en DMF seco (2mL) bajo una atmósfera de nitrógeno. Se agregó 1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-amina (188mg, 0.674mmol), seguida por TEA (68mg, 0.667mmol), y la mezcla de reacción se calentó en un reactor microondas a 120°C durante 20 minutos. La mezcla de reacción se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ acuoso saturado, se secó sobre Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó en un sistema HPFC Biotage Horizon usando heptano y EtOAc como eluyente, lo cual proporcionó el compuesto del título (284mg, 77.6%). ^{1}HNMR (500 MHz, $CDCl_3$): δ 1.46-1.54 (m, 2H), 1.73-1.79 (m, HH), 2.51 (t, 2H), 3.12-3.19 (m, 1H), 3.79-3.82 (m, 2H), 5.28

(d, 1H), 7.44-7.46 (m, 3H), 7.53-7.55 (m, 2H), 7.72 (s, 1H), 8.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.82, 32.36, 47.43, 50.27, 61.80, 107.32, 120.35 (q, J=33.4Hz), 121.28, 123.48 (q, J=271.3Hz), 125.36, 128.94, 130.17, 131.85, 134.16, 136.15, 143.10, 159.87, 160.06; Espectro de Masa: $M+H^+$ 543.1.

Ejemplo 80

***terc*-Butil 3-{2-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}azetidin-1-carboxilato**

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (74mg, 0.249mmol) se disolvió en DMF seco (1mL) bajo una atmósfera de nitrógeno. *terc*-Butil 3-(2-aminoetil)azetidin-1-carboxilato (50mg, 0.249mmol) se agregó, seguido por TEA (25mg, 0.247mmol), y la mezcla de reacción se calentó en un reactor microondas a 120°C durante 20 minutos. La mezcla de reacción se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ acuoso saturado, se secó sobre Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó por HPLC preparativa, lo cual proporcionó el compuesto del título (33mg, 28.8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.62 (q, 2H), 1.73 (s, 9H), 2.19-2.27 (m, 1H), 2.83 (q, 2H), 3.23-3.26 (m, 2H), 3.84 (t, 2H), 5.25 (t, 1H), 7.42-7.51 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.24, 27.82, 28.61, 34.35, 41.72, 54.06, 61.82, 79.63, 107.55, 125.15, 128.93, 130.09, 131.79, 135.04, 156.38, 159.81; Espectro de Masa: $M-H^+$ 462.

Ejemplo 81

4-{2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), 4-(2-aminoetil)benzonitrilo (0.101g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.039g,

16%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.43 (m, 7H), 6.88-6.84 (m, 2H), 5.39-5.33 (m, 1H), 3.17- 3.10 (m, 2H), 2.65-2.60 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 143.2, 134.7, 132.7, 131.8, 130.1, 129.5, 129.1, 125.2, 118.8, 111.1, 108.1, 61.9, 44.5, 41.2, 36.2, 27.8; Espectro de Masa: M-H^+ 410.

Ejemplo 82

1,1-Dióxido de 2-*terc*-butil-4-(isopropilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisomiazol-3(2*H*)-ona (0.175g, 0.58mmol), isopropilamina (0.041g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.108g, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.46 (m, 2H), 7.44-7.38 (m, 3H), 5.16-5.04 (m, 1H), 3.34-3.22 (m, 1H), 1.71 (s, 9H), 0.94 (d, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 134.2, 131.7, 129.8, 128.9, 125.6, 106.5, 61.6, 44.8, 27.8, 23.0; Espectro de Masa: M-H^+ 323.

Ejemplo 83

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-2-iloxi)propil]amino} isotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 24 de 1 equivalente de [3-(piridin-2-iloxi)propil]amina, 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1 equivalente de TEA con un tiempo de reacción de 30 minutos. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 5:1 éter de petróleo 40-60°C en EtOAc como eluyente para producir el compuesto del título (0.178g, 65%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 8.17 (dd, 1H), 7.62-7.57 (m, 1H), 7.54-7.48 (m, 2H), 7.45-7.40 (m, 3H), 6.91-6.88 (m, 1H), 6.74 (d, 1H), 6.00 (t, 1H), 4.28 (t, 2H), 3.04 (q, 2H), 1.83 (quintete, 2H), 1.75 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): δ 163.8, 159.9, 147.0,

138.9, 135.5, 131.8, 129.7, 128.8, 125.4, 117.3, 111.5, 106.9, 63.6, 61.6, 42.0, 28.9, 27.9; Espectro de Masa: $M+H^+$ 416.

Ejemplo 84

1,1-Dióxido de 2-*terc*-butil-4-{[1-(5-metilpiridin-2-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (97mg, 0.324mmol) se disolvió en DMF seco (1mL) bajo una atmósfera de nitrógeno. Se agregó clorhidrato de 1-(5-metilpiridin-2-il)piperidin-4-amina (86mg, 0.327mmol), seguido por TEA (33g, 0.324mmol). La mezcla de reacción se calentó en un reactor microondas a 120°C durante 25minutos. La mezcla se diluyó con EtOAc y se lavó con solución de $NaHCO_3$ acuoso saturado y agua. La fase orgánica se secó sobre Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó por HPLC preparativa, lo cual proporcionó el compuesto del título (64mg, 43.5%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.33-1.41 (m, 2H), 1.71-1.74 (m, 11H), 2.17 (s, 3H), 2.38-2.43 (m, 2H), 3.08- 3.15 (m, 1H), 3.95-3.99 (m, 2H), 5.23 (d, 1H), 6.51 (d, 1H), 7.26 (dd, 1H), 7.43-7.45 (m, 3H), 7.53-7.55 (m, 2H), 7.96 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.51, 27.84, 32.05, 44.64, 50.68, 61.78, 107.10, 107.50, 122.63, 125.39, 128.91, 130.11, 131.90, 134.20, 138.65, 147.86, 157.77, 159.91; Espectro de Masa: $M+H^+$ 455.0.

Ejemplo 85

1,1-Dióxido de 2-*terc*-butil-4-{[1-(6-cloropiridazin-3-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.450g, 1.50mmol), 1-(6-cloropiridazin-3-il)piperidin-4-amina (0.487g, 1.95mmol) y TEA (0.456g, 4.50mmol) se disolvieron en MeCN seco (15 ml) y se calentaron en un reactor microondas a 120°C durante 30 minutos. La mezcla de reacción se evaporó, y el residuo se diluyó con EtOAc (150 ml) y se lavó con agua (500 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se evaporó. El residuo se purificó por cromatografía en columna de gel de

sílice usando una mezcla 60:40→50:50 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.191g, 27%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.47-7.43 (m, 3H), 7.15 (d, 1H), 6.81 (d, 1H), 5.20 (d, 1H), 4.11-4.05 (m, 2H), 3.22-3.13 (m, 1H), 2.60-2.52 (m, 2H), 1.80-1.73 (m, 2H), 1.72 (s, 9H), 1.41-1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 158.6, 147, 133.8, 131.6, 130, 128.8, 128.7, 125, 115.4, 107.3, 61.6, 50, 43.8, 31.6, 27.6.

Ejemplo 86

***terc*-Butil 4-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-carboxilato**

Una mezcla de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (2.000g, 6.672mmol), *terc*-butil 4-aminopiperidin-1-carboxilato (1.336g, 6.672mmol) y TEA (0.933ml, 6.672mmol) en MeCN (20ml) se calentó en un reactor microondas a 120°C durante 40 minutos y 130°C durante 30 minutos. Se agregaron *terc*-butil 4-aminopiperidin-1-carboxilato (0.267mg, 1.334mmol) y TEA (0.187ml, 1.334mmol), y la mezcla resultante se calentó en un reactor microondas a 120°C durante 20minutos. La mezcla de reacción se evaporó a sequedad, y el residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) eluyendo con 10% éter de petróleo 40-60°C en DCM, luego 0-20% EtOAc en DCM para producir el compuesto del título (2.228g, 72%) como un sólido. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.44 (m, 3H), 5.17 (d, 1H), 3.88 (bs, 2H), 3.08-3.00 (m, 1H), 2.32 (dt, 2H), 1.74 (s, 9H), 1.68-1.60 (m, 2H), 1.42 (s, 9H), 1.30-1.17 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.8, 154.7, 134.1, 131.9, 130.2, 128.9, 125.3, 107.3, 80.1, 61.9, 50.4, 42.4, 32.4, 28.6, 27.9; Espectro de Masa $M+H^+$ 464.

Ejemplo 87

1,1-Dióxido de 2-*terc*-butil-4-{[1-(6-metoxipiridazin-3-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.300g, 1.00mmol), diclorhidrato de 1-(6-metoxipiridazin-3-il)piperidin-4-amina (0.349g, 1.24mmol) y TEA (0.405g, 4.00mmol) se disolvieron en DMF seco (10 ml) y se calentaron en un reactor microondas a 120°C durante 30 minutos. La mezcla de reacción se diluyó con agua (200 ml) y se extrajo con EtOAc (200 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se evaporó. El residuo se purificó por cromatografía en columna de gel de sílice usando una mezcla 55:45 de heptano y EtOAc como eluyente, para producir el compuesto del título (0.232g, 49%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.46-7.41 (m, 3H), 6.92 (d, 1H), 6.79 (d, 1H), 5.2 (d, 1H), 4.00 (s, 3H), 3.93-3.87 (m, 2H), 3.17-3.08 (m, 1H), 2.53-2.45 (m, 2H), 1.77-1.71 (m, 2H), 1.72 (s, 9H), 1.44-1.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 159.6, 157.3, 133.8, 131.6, 129.9, 128.7, 125, 119.4, 119.1, 107, 61.6, 54.3, 50.1, 45.1, 31.6, 27.6; Espectro de Masa: M-H$^+$ 472.

Ejemplo 88

1,1-Dióxido de 2-*terc*-butil-4-{[1-(6-cloropiridin-3-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), diclorhidrato de 1-(6-cloropiridin-3-il)piperidin-4-amina (0.196g, 0.69mmol) y TEA (0.23 g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó con HPLC preparativa, lo cual produjo el compuesto del título (0.022g, 8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92-7.87 (m, 1H), 7.55-7.48 (m, 2H), 7.48-7.41 (m, 3H), 7.13-7.03 (m, 2H), 5.24-5.18 (m, 1H), 3.45-3.35 (m, 2H), 3.13-3.01 (m, 1H), 2.39-2.29 (m, 2H), 1.82-1.71 (m, 2H), 1.73 (s, 9H), 1.52-1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 145.8, 141.7, 138.0, 134.1, 131.8, 130.2, 129.0, 126.6, 125.3, 124.1, 107.5, 15 61.9, 49.8, 47.8, 32.0, 27.8; Espectro de Masa: M-H$^+$ 475.

Ejemplo 89

1,1-Dióxido de 4-[(1-bencilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 24 de 1 equivalente de 1-bencilpiperidin-4-amina, 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1 equivalente de TEA con un tiempo de reacción de 30 minutos. El residuo se purificó por cromatografía en columna de gel de sílice (Horizons Biotage) usando 35% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.132g, 58%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.7.47 (m, 2H), 7.46-7.42 (m, 3H), 7.31-7.26 (m, 2H), 7.26-7.21 (m, 3H), 5.20 (d, 1H), 3.35 (s, 2H), 2.99-2.90 (m, 1H), 2.67-2.62 (m, 2H), 1.74 (s, 9H), 1.71-1.56 (m, 4H), 1.44-1.33 (m, 2H); 13C NMR (125MHz $CDCl_3$): δ 159.9, 138.5, 134.2, 131.8, 129.9, 129.1, 128.8, 128.4, 127.3, 125.4, 106.7, 62.9, 61.7, 51.9, 50.3, 32.6, 27.8; Espectro de Masa: $M+H^+$ 454.

Ejemplo 90

1,1-Dióxido de 2-*terc*-butil-4-(etilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), clorhidrato de etilamina (0.056g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.099g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.46 (m, 2H), 7.43-7.38 (m, 3H), 5.21-5.12 (m, 1H), 2.89- 2.80 (m, 2H), 1.72 (s, 9H), 1.01 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 135.2, 131.7, 129.7, 128.7, 125.4, 107.1, 61.7, 39.3, 27.8, 15.0; Espectro de Masa: $M-H^+$ 309.

Ejemplo 91

N-2-(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-N-1-[3-(difluorometoxi)bencil]glicinamida

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), N-[3-(difluorometoxi)bencil]glicinamida (0.159g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.118g, 41%). ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.46-7.35 (m, 5H), 7.35-7.28 (m, 1H), 7.09-7.01 (m, 2H), 6.99-6.94 (m, 1H), 6.50 (t, 1H), 6.02-5.94 (m, 1H), 5.91-5.82 (m, 1H), 4.37-4.31 (m, 2H), 3.53-3.48 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 159.3, 139.9, 134.9, 131.5, 130.5, 130.2, 129.0, 125.1, 124.5, 119.4, 119.0, 116.0, 113.9, 109.9, 62.0, 46.8, 43.4, 27.8; Espectro de Masa: M-H$^+$ 494.

Ejemplo 92

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(1-piridin-2-ilpiperidin-4-il)amino]isotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), diclorhidrato de 1-piridin-2-ilpiperidin-4-amina (0.173g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.175g, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08-8.03 (m, 1H), 7.50-7.44 (m, 2H), 7.41- 7.32 (m, 4H), 6.55-6.47 (m, 2H), 5.28-5.20 (m, 1H), 4.02-3.93 (m, 2H), 3.11-3.00 (m, 1H), 2.41-2.30 (m, 2H), 1.73-1.60 (m, 2H), 1.67 (s, 9H), 1.36-1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 159.1, 148.0, 137.7, 134.2, 131.9, 130.1, 128.9, 125.4, 113.5, 107.5, 107.0,
30 61.7, 50.7, 44.1, 41.2, 32.0, 27.8; Espectro de Masa: M-H$^+$ 441.

Ejemplo 93

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(1-piridazin-3-ilpiperidin-4-il)amino]isotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.240g, 0.80mmol), 1-piridazin-3-ilpiperidin-4-amina (0.257g, 1.02mmol) y TEA (0.324g, 3.2mmol), se disolvieron en DMF seco (10 ml) y se calentaron en un reactor microondas a 120°C durante 30 minutos. La mezcla de reacción se diluyó con agua (300 ml) y se extrajo con EtOAc (2x150 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se evaporaron, y el residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc como eluyente, para producir el compuesto del título (0.110g, 31%). ^{1}HNMR (500 MHz, $CDCl_3$): δ 8.55-8.52 (m, 1H), 7.55-7.50 (m, 2H), 7.47-7.42 (m, 3H), 7.19-7.14 (m, 1H), 6.85-6.82 (m, 1H), 5.21 (d, 1H), 4.17-4.11 (m, 2H), 3.22-3.13 (m, 1H), 2.60-2.52 (m, 2H), 1.80-1.73 (m, 2H), 1.72 (s, 9H), 1.42-1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 143.1, 133.8, 131.6, 129.9, 128.7, 127.4, 125, 112.8, 107.2, 61.6, 50.1, 43.6, 31.7, 27.5; Espectro de Masa: M-H^+ 442.

Ejemplo 94

1,1-Dióxido de 2-*terc*-butil-4-{[1-(5-fluoropiridin-2-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)- ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), diclorhidrato de 1-(5-fluoropiridin-2-il)piperidin-4-amina (0.155g, 0.58mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.153g, 58%). ^{1}HNMR (500 MHz, $CDCl_3$): δ 8.01-7.95 (m, 1H), 7.56-7.49 (m, 2H), 7.48-7.39 (m, 3H), 7.23-7.16 (m, 1H), 6.56-6.48 (m, 1H), 5.25-5.15 (m, 1H), 3.98-3.86 (m, 2H), 3.17-3.04 (m, 1H), 2.47-2.36 (m, 2H), 1.80-1.64 (m, 2H), 1.72 (s, 9H), 1.43-1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 156.1, 154.7, 152.7, 134.8, 134.6, 134.1, 131.9, 130.1, 128.9, 125.3, 108.3, 107.3, 61.8, 50.5, 45.0, 32.0, 27.8; Espectro de Masa: M-H^+ 459.

Ejemplo 95

1,1-Dióxido de 2-*terc*-butil-4-{[3-(3,5-dimetil-1H-pirazol-1-il)propil] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (150 mg, 0.5 mmol), tartrato de 3-(3,5-dimetil-pirazol-1-il)-propilamina (167 mg, 0.55 mmol) se mezclaron en MeCN (3 ml). Se agregó trietilamina (0.23 ml, 1.65 mmol), y la mezcla se calentó en un reactor microondas a 120°C durante 15 minutos. La mezcla de reacción se evaporó a sequedad, y el residuo se purificó por cromatografía en columna (ISOLUTE SI, 20g/70ml), eluyendo con DCM y luego con MeOH/DCM (1:99), para producir el compuesto del título (195 mg, 94%). ^{1}H NMR (400 MHz, CDCl3): δ 1.70 (s, 9H), 1.72-1.79 (m, 2H), 2.05 (s, 3H), 2.18 (s, 3H), 2.81-2.86 (m, 2H), 3.79 (t, 2H), 5.71 (bs, 2H), 7.37-7.46 (m, 5H); ^{13}C NMR (100 MHz, CDCl3): δ 10.8, 13.4, 27.5, 29.2, 41.5, 45.4, 61.3, 105.1, 106.8, 125.0, 128.4, 129.4, 131.4, 135.0, 138.5, 147.7, 159.3; Espectro de Masa: M+H$^+$ 417.

Ejemplo 96

1,1-Dióxido de 2-*terc*-butil-4-{[1-(5-cloropiridin-2-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), diclorhidrato de 1-(5-cloropiridin-2-il)piperidin-4-amina (0.196g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.124g, 45%). ^{1}HNMR (500 MHz, $CDCl_3$): δ 8.06-8.02 (m, 1H), 7.55-7.49 (m, 2H), 7.47- 7.41 (m, 3H), 7.39-7.33 (m, 1H), 6.52-6.45 (m, 1H), 5.24-5.14 (m, 1H), 4.02-3.93 (m, 1H), 3.18-3.06 (m, 1H), 2.49-2.39 (m, 2H), 1.78-1.66 (m, 2H), 1.72 (s, 9H), 1.39-1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 157.4, 146.3, 137.5, 134.1, 131.9, 130.2, 128.9, 125.3, 120.5, 108.2, 107.3, 61.9, 50.5, 44.3, 32.0, 27.8; Espectro de Masa: M-H$^+$ 475.

Ejemplo 97

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-({1-[4-(trifluorometil)piridin-2-il]piperidin-4-il}amino)isotiazol-3(2*H*)-ona

1,1-Dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (0.175g, 0.58mmol), diclorhidrato de 1-[4-(trifluorometil)piridin-2-il]piperidin-4-amina (0.220g, 0.69mmol) y TEA (0.23g, 2.31mmol) se disolvieron en DMF seco (3 ml) y se calentaron en un reactor microondas a 130°C durante 30 minutos. La mezcla de reacción se purificó por HPLC preparativa para proporcionar el compuesto del título (0.112g, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28-8.23 (m, 1H), 7.59-7.52 (m, 2H), 7.51-7.44 (m, 3H), 6.79-6.74 (m, 1H), 6.74-6.70 (m, 1H), 5.27-5.17 (m, 1H), 4.17- 4.07 (m, 2H), 3.24-3.13 (m, 1H), 2.57-2.48 (m, 2H), 1.83-1.69 (m, 2H), 1.75 (s, 9H), 1.42- 1.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 149.3, 134.1, 131.9, 130.2, 129.0, 125.3, 108.5, 107.4, 102.9, 61.9, 50.5, 43.9, 32.0, 27.8; Espectro de Masa: M-H^+ 509.

Ejemplo 98

1,1-Dióxido de 2-*terc*-butil-4-(*terc*-butilamino)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 24 de 1,1-dióxido de *terc*-butilamina y 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona a 140°C durante 1.5 horas. El residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 0-5% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.029g, 17%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ .54-7.50 (m, 2H), 7.48-7.44 (m, 3H), 5.53 (s, 1H), 1.74 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): 160.9, 133.8, 133.5, 130.3, 129.1, 126.8, 106.6, 10 61.8, 52.2, 30.1, 27.8; Espectro de Masa: M+H^+ 337.

Ejemplo 99

2-{2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenil metanosulfonato

2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] etil 4-metilbencenosulfonato (150mg, 0.313mmol) se disolvió en MeCN seco (3mL) bajo una atmósfera de nitrógeno. Se agregó 2-hidroxifenil metanosulfonato (65mg, 0.345mmol), seguido por carbonato de potasio (217mg, 1.567mmol). La mezcla de reacción se calentó en un reactor microondas a 120°C durante 15 minutos. Carbonato de potasio se filtró completamente, y la mezcla de reacción se evaporó a sequedad en una centrífuga de vacío. El producto crudo se purificó por HPLC preparativa, proporcionando el compuesto del título (94mg, 58.5%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.71 (s, 9H), 3.19 (s, 3H), 3.26 (q, 2H), 3.92 (t, 2H), 5.86 (t, 1H), 6.86 (d, 1H), 6.99 (t, 1H), 7.22 (t, 1H), 7.28 (d, 1H), 7.42-7.45 (m, 3H), 7.49-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.82, 38.53, 43.28, 61.78, 67.18, 108.11, 114.66, 122.30, 124.66, 125.15, 128.54, 129.08, 130.04, 131.69, 135.27, 138.61, 150.49, 159.51; Espectro de Masa: $M+H^+$ 494.8.

Ejemplo 100

***terc*-Butil 3-({2-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}tio)pirrolidin-1-carboxilato**

2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil 4-metilbencenosulfonato (150mg, 0.313mmol) se disolvió en MeCN seco (3mL) bajo una atmósfera de nitrógeno. Se agregó *terc*-butil 3-mercaptopirrolidin-1-carboxilato (70mg, 0.345mmol), seguido por carbonato de potasio (217mg, 1.567mmol). La mezcla de reacción se calentó en un reactor microondas a 120°C durante 15 minutos. Carbonato de potasio se filtró completamente, y la mezcla de reacción se evaporó a sequedad en una centrífuga de vacío. El producto crudo se purificó por HPLC preparativa proporcionando el compuesto del título (134mg, 83.4%). El producto es una mezcla de cis y trans isómeros. ^{1}H NMR ($CDCl_3$,

500MHz): δ 1.47 (s, 9H), 1.73 (s, 10H), 2.05 (s, 1H), 2.46-2.51 (m, 2H), 2.88 (bs, 1H), 3.01-3.13 (m, 3H), 3.29 (s, 1H), 3.41-3.57 (m, 2H), 5.65 (bs, 1H), 7.43-7.46 (m, 3H), 7.49-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.83, 28.73, 31.29, 32.33, 32.86, 41.74, 42.41, 43.23, 44.86, 45.09, 52.27, 52.53, 61.86, 79.79, 108.04, 125.15, 129.04, 130.04, 131.65, 134.81, 154.41, 159.66; Espectro de Masa: $M+H^+$ 509.9.

Ejemplo 101

Metil 2-{2-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etoxi}benzoato

2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil 4-metilbencenosulfonato (150mg, 0.313mmol) se disolvió en MeCN seco (3mL) bajo una atmósfera de nitrógeno. Se agregó salicilato de metilo (52mg, 0.345mmol), seguido por carbonato de potasio (217mg, 1.567mmol). La mezcla de reacción se calentó en un reactor microondas a 120°C durante 20 minutos. Carbonato de potasio se filtró completamente y la mezcla de reacción se evaporó a sequedad en una centrífuga de vacío. El producto crudo se purificó por HPLC preparativa proporcionando el compuesto del título (9mg, 6%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.74 (s, 9H), 3.27 (q, 2H), 3.97-4.00 (m, 5H), 6.17 (t, 1H), 6.86 (d, 1H), 7.05 (t, 1H), 7.44-7.48 (m, 4H), 7.52-7.56 (m, 2H), 7.85 (dd, 1H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.85, 43.53, 52.52, 61.69, 67.49, 107.84, 114.40, 121.12, 121.69, 125.42, 129.00, 129.85, 131.69, 132.27, 133.85, 135.56, 158.01, 159.56, 166.79; Espectro de Masa: $M+H^+$ 459.0.

Ejemplo 102

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[2-(piridin-3-iloxi)etil]amino} isotiazol-3(2*H*)-ona

2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil 4-metilbencenosulfonato (150mg, 0.313mmol) se disolvió en MeCN seco (3mL) bajo una atmósfera de nitrógeno. Se agregó piridin-3-ol (33mg, 0.345mmol), seguido por carbonato de potasio (217mg,

1.567mmol). La mezcla de reacción se calentó en un reactor microondas a 120°C durante 15 minutos. Carbonato de potasio se filtró completamente y la mezcla de reacción se evaporó a sequedad en una centrífuga de vacío. El producto crudo se purificó por HPLC preparativa proporcionando el compuesto del título (46mg, 35.7%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.74 (s, 9H), 3.30 (q, 2H), 3.92 (t, 2H), 5.64 (t, 1H), 7.12-7.14 (m, 1H), 7.22-7.24 (m, 1H), 7.46-7.48 (m, 3H), 7.53-7.55 (m, 2H), 8.26-8.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.84, 43.32, 61.90, 66.37, 108.51, 121.55, 124.15, 125.03, 129.09, 130.10, 131.69, 135.11, 137.90, 143.23, 154.51, 159.64; Espectro de Masa: $M+H^+$ 402.1.

Ejemplo 103

4-{2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenil metanosulfonato

2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil 4-metilbencenosulfonato (150mg, 0.313mmol) se disolvió en MeCN seco (3mL) bajo una atmósfera de nitrógeno. Se agregó 4-hidroxifenil metanosulfonato (65mg, 0.345mmol), seguido por carbonato de potasio (217mg, 1.567mmol). La mezcla de reacción se calentó en un reactor microondas a 120°C durante 15 minutos. Carbonato de potasio se filtró completamente y la mezcla de reacción se evaporó a sequedad en una centrífuga de vacío. El producto crudo se purificó por HPLC preparativa proporcionando el compuesto del título (61mg, 38.5%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.73 (s, 9H), 3.11 (s, 3H), 3.23-3.27 (m, 2H), 3.83-3.86 (m, 2H), 5.65 (bs, 1H), 6.83 (d, 2H), 7.20 (d, 2H), 7.43-7.46 (m, 3H), 7.50-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.83, 37.34, 43.30, 61.85, 66.50, 108.27, 115.77, 123.48, 125.07, 129.07, 130.06, 131.68, 135.18, 143.35, 157.21, 159.65; Espectro de Masa: $M+NH_4^+$ 511.8.

Ejemplo 104

4-({4-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}metil)benzonitrilo

Una mezcla de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) (0.100g, 0.275mmol), 4-(bromometil)benzonitrilo (0.054g, 0.275mmol), 1-bencil-1,3,4,6,7,8-hexahidro-2H-pirimido[1,2-*a*]pirimidina en polistireno (0.055g, 0.413mmol) en DMF (2ml) se calentó en un reactor microondas a 150°C durante 7 minutos. La mezcla de reacción se filtró, se evaporó a sequedad, y el residuo se purificó por HPLC preparativa para producir el compuesto del título (0.040g, 30%); ^{1}H NMR (500MHz $CDCl_3$): δ 7.59 (d, 2H), 7.52-7.49 (m, 2H), 7.48-7.42 (m, 3H), 7.37 (d, 2H), 5.21 (d, 1H), 3.41 (s, 2H), 3.01-2.90 (m, 1H), 2.65-2.56 (m, 2H), 1.74 (s, 9H), 1.69-1.60 (m, 4H), 1.44-1.34 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 144.5, 134.2, 132.3, 131.9, 129.9, 129.4, 128.9, 125.4, 119.1, 111.1, 106.9, 62.3, 61.8, 51.9, 50.1, 32.5, 27.8; Espectro de Masa $M+H^+$ 479.

Ejemplo 105

1,1-Dióxido de 2-*terc*-nutil-5-fenil-4-({1-[2-(trifluorometil)benzoil] piperidin-4-il} amino) isotiazol-3(2*H*)-ona

Una mezcla de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) (0.100g, 0.275mmol), cloruro de 2-(trifluorometil) benzoilo (0.049ml, 0.330mmol) y 2-*terc*-butilimino-2-dietilamino-1,3-dimetil-perhidro-1,3,2-diazafosforina en polistireno (0.600g, 1.376mmol) en DCM (2ml) se agitó a temperatura de la sala durante 17 horas. La mezcla se filtró, se evaporó a sequedad, y el residuo se purificó por HPLC preparativa para producir el compuesto del título (0.053g, 36%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.68 (t, 1H), 7.61-7.42 (m, 6h), 7.26 (d, 1H), 7.18 (d, 1H), 5.21 (d, 1H), 4.61-4.46 (m, 1H), 3.24-3.10 (m, 2H), 2.54-2.38 (m, 2H), 1.88-1.78 (m, 1H), 1.76-1.48 (10H), 1.44-1.32 (m, 1H), 1.26-1.10 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 167.4, 167.3, 159.8, 159.7, 134.8, 133.9, 133.8, 132.5, 132.3, 131.9, 131.7, 130.4, 130.2,

129.5, 129.0, 128.9, 127.3, 127.0, 126.9, 125.3, 125.1, 107.8, 107.5, 61.9, 50.3, 50.1, 45.7, 45.5, 41.2, 40.3, 40.1, 32.5, 32.1, 31.9, 31.8, 27.8; Espectro de Masa: M-H^+ 534

Ejemplo 106

Metil 3-({4-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-il}metil)benzoato

El compuesto del título se preparó como se describe para Ejemplo 104 de metil 3-(bromometil)benzoato y 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) para producir el compuesto del título (0.101g, 48%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 7.95-7.87 (m, 2H), 7.54-7.32 (m, 7H), 5.20 (d, 1H), 3.92 (s, 3H), 3.38 (s, 2H), 3.00-2.80 (m, 1H), 2.66-2.58 (m, 2H), 1.80-1.54 (m, 13H), 1.42-1.30 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 167.4, 159.9, 139.1, 134.3, 133.6, 131.8, 130.4, 130.2, 129.9, 128.8, 128.6, 125.4, 106.8, 62.5, 61.8, 52.3, 51.9, 50.2, 32.5, 27.8; Espectro de Masa: M+H^+ 512.

Ejemplo 107

1,1-Dióxido de 2-*terc*-butil-4-({1-[(2-cloropiridin-3-il)carbonil] piperidin-4-il} amino)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 105 de cloruro de 2-cloronicotinilo y 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino) isotiazol-3(2*H*)-ona (Ejemplo 75) para producir el compuesto del título (0.03Og, 22%). ^{1}H NMR (500MHz $CDCl_3$): δ 8.46-8.42 (m, 1H), 7.62 (d, 1H), 7.58-7.44 (m, 5H), 7.37-7.26 (m, 1H), 7.52 (dd, 1H), 3.30-3.10 (m, 2H), 2.73-2.40 (m, 5H), 1.90-1.80 (m, 1H), 1.74 (s, 9H), 1.68-1.58 (m, 2H), 1.54-1.10 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 165.2, 165.1, 159.7, 159.6, 150.5, 150.3, 147.3, 137.0, 136.9, 133.9, 133.8, 132.3, 132.1, 131.9, 131.7,1 130.4, 130.2, 129.1, 128.9, 125.3, 125.0, 10 123.0, 122.9, 108.1, 107.7, 61.9, 50.3, 49.9, 45.7, 44.9, 40.4, 40.2, 32.8, 32.7, 32.0, 31.9, 27.8; Espectro de Masa: M-H^+ 503.

Ejemplo 108

1,1-Dióxido de 2-*terc*-butil-4-({1-[(5-metilisoxazol-3-il)metil]piperidin-4-il}amino)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 104 de 3-(bromometil)-5-metilisooxazol y 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) para producir el compuesto del título (0.021g, 17%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.48-7.42 (m, 3H), 5.92 (s, 1H), 5.18 (d, 1H), 3.40 (s, 2H), 2.98-2.88 (m, 1H), 2.70-2.62 (m, 2H), 2.40 (s, 3H), 1.74 (m, 9H), 1.79-1.60 (m, 4H), 1.42- 1.32 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 169.7, 161.7, 159.9, 134.2, 131.8, 130.1, 128.9, 125.3, 106.9, 101.8, 61.8, 53.4, 52.0, 50.1, 32.5, 27.8, 12.5; Espectro de Masa $M+H^+$ 459.

Ejemplo 109

1,1-Dióxido de 4-[(1-benzoilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

Una mezcla de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) (0.150mg, 0.413mmol), ácido benzoico (0.055g, 0.454mmol), EDC (0.087g, 0.454mmol), HOBt (0.061g, 0.454mmol) y TEA (0.120ml, 0.825mmol) en THF (3ml) se agitó a temperatura de la sala durante 3.5 horas. La mezcla de reacción se evaporó, y el residuo se purificó cromatografía en columna en gel de sílice (Horizons Biotage) usando 50% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.136g, 71%) como un sólido. ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.42 (m, 5H), 7.42-7.35 (m, 2H), 7.32-7.29 (m, 1H), 5.21 (d, 1H), 4.48 (bs, 1H), 3.56 (bs, 1H), 3.24-3.12 (m, 1H), 2.58-2.44 (m, 2H), 1.90-1.64 (bs, 2H), 1.74 (s, 9H), 1.48-1.16 (bs, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 170.6, 159.7, 135.7, 133.9, 131.8, 130.2, 130.0, 128.9, 128.7, 126.9, 125.2, 107.7, 61.9, 50.4, 27.8; Espectro de Masa: $M+H^+$ 468.

Ejemplo 110

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[1-(fenilacetil)piperidin-4-il] amino}isotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 105 de cloruro fenilacético y 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino) isotiazol-3(2*H*)-ona (Ejemplo 75) para producir el compuesto del título (0.103g, 78%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.47 (m, 2H), 7.47-7.41 (m, 3H), 7.34-7.29 (m, 2H), 7.27-7.23 (m, 1H), 7.18 (d, 2H), 5.12 (d, 1H), 4.43-4.26 (m, 1H), 3.70-3.61 (m, 3H), 3.11-3.02 (m, 1H), 2.55-2.47 (m, 1H), 2.28-2.20 (m, 1H), 1.90-1.65 (m, HH), 1.54-1.47 (m, 1H), 1.19 (dq, 1H), 0.91 (dq, 1H); ^{13}C δ NMR (125MHz $CDCl_3$): 169.5, 159.7, 135.0, 133.9, 131.8, 130.2, 129.0, 128.9, 128.6, 127.2, 125.2, 107.5, 61.9, 50.2, 44.6, 41.3, 41.2, 40.4, 32.6, 32.1, 27.8; Espectro de Masa: $M+H^+$ 482.

Ejemplo 111

1,1-Dióxido de 2-*terc*-butil-4-{[1-(2-cloro-6-metilisonicotinoil)piperidin-4-il]amino}-5- fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 105 de cloruro de 2-cloruro-6-metilisonicotinoilo y 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) usando DMAP como catalizador y DMF como disolvente. Se agregó EtOAc a la mezcla de reacción, y se lavó con salmuera, se evaporó, y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 50% EtOAc en éter de petróleo 40-60°C como eluyente para producir el compuesto del título (0.037g, 26%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.43 (m, 3H), 7.02 (s, 1H), 6.96 (s, 1H), 5.21 (d, 1H), 4.48-4.38 (m, 1H), 3.46-3.36 (m, 1H), 3.24-3.14 (m, 1H), 2.62-2.40 (m, 5H), 1.90-1.80 (m, 1H), 1.74 (s, 9H), 1.70-1.60 (m, 1H), 1.44-1.32 (m, 1H), 1.30-1.18 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 166.7, 160.7, 159.7, 151.3, 146.6, 133.9, 131.8, 130.3, 129.0, 125.2, 119.3, 118.6, 107.9, 61.9, 50.1, 45.8, 41.1, 40.7, 32.9, 31.9, 27.8, 24.5; Espectro de Masa: $M+H^+$ 517.

Ejemplo 112

4-({4-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}carbonil)benzonitrilo

El compuesto del título se preparó como se describe para Ejemplo 105 de cloruro de 4-cianobenzoilo y 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino) isotiazol-3(2*H*)-ona (Ejemplo 75) usando DMF como disolvente. La mezcla de reacción se evaporó, y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 50% EtOAc en éter de petróleo 40-60°C como eluyente. El producto que contenía las fracciones se evaporó, se disolvió en DCM, se lavó a través de una columna de intercambio catiónico y se evaporó para producir el compuesto del título (0.015g, 11%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.70 (d, 1H), 7.55-7.50 (m, 2H), 7.49-7.40 (m, 5H), 5.21 (d, 1H), 4.52-4.40 (m, 1H), 3.50-3.36 (m, 1H), 3.24-3.14 (m, 2H), 2.62-2.44 (m, 2H), 1.92-1.78 (m, 1H), 1.74 (s, 9H), 1.67-1.54 (m, 2H), 1.48-1.16 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 168.5, 159.7, 140.1, 133.9, 132.7, 131.8, 130.3, 129.0, 127.7, 125.2, 118.2, 113.9, 107.9, 61.9, 50.1, 46.0, 40.9, 32.9, 32.1, 27.8; $M+H^+$ 493.

Ejemplo 113

1,1-Dióxido de 2-*terc*-butil-4-{[1-(3,4-difluorobenzoil)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 105 de cloruro de 3,4-difluorobenzoilo y 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino) isotiazol-3(2*H*)-ona (Ejemplo 75) para producir el compuesto del título (0.033g, 24%). ^{1}H NMR (500MHz $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.48-7.42 (m, 3H), 7.22-7.14 (m, 2H), 7.10-7.04 (m, 1H), 5.23 (d, 1H), 4.40 (bs, 1H), 3.58 (bs, 1H), 3.22-3.12 (m, 1H), 2.58-2.46 (m, 2H), 1.80-1.60 (m, 11H), 1.42-1.14 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 168.3, 159.7, 152.6, 152.4, 151.6, 151.4, 150.6, 150.4, 149.6, 149.4, 133.9, 132.5, 131.8, 130.3, 129.0, 125.2, 123.7, 117.9, 117.8, 116.9, 116.8, 107.8, 61.9, 50.2, 46.0, 32.5, 27.8; Espectro de Masa: $M-H^+$ 502.

Ejemplo 114

4-{2-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenil metanosulfonato

Una mezcla de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.15g, 0.52mmol), 4-(2-aminoetil)fenil metanosulfonato (0.14g, 0.63mmol) y TEA (0.07g, 0.68mmol) en MeCN (1.5ml) se calentó en un reactor microondas a 120°C durante 35 minutos. 4-(2-Aminoetil)fenil metanosulfonato (0.07g) se agregó a la mezcla, y se calentó en un reactor microondas a 120°C durante 20 minutos. La mezcla de reacción se evaporó, y el producto crudo se purificó por cromatografía rápida en columna usando hexano y EtOAc, 80:20-30:70, como eluyente para proporcionar el compuesto del título (0.21g, 85%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.57-1.59 (m, 6H), 2.50-2.61 (m, 2H), 3.12-3.16 (m, 5H), 4.39-4.42 (m, 1H), 5.23 (him, 1H), 5 6.80-6.83 (m, 2H), 7.12-7.15 (m, 2H), 7.48-7.54 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$): δ 14.4, 20.4, 35.5, 37.6, 45.0, 47.8, 107.8, 122.4, 125.2, 129.1, 130.1, 130.3, 131.8, 135.2, 137.0, 148.2, 158.6; Espectro de Masa: M-H^+ 463.

Ejemplo 115

4-{2-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}bencenosulfonamida

Una mezcla de 1,1-dióxido de 4-cloro-2-isopopil-5-fenilisotiazol-3(2*H*)-ona (0.16g, 0.56mmol), 4-(2-aminoetil)bencenosulfonamida (0.14g, 0.67mmol) y TEA (0.07g, 0.73mmol) en MeCN (1.5ml) se calentó en un reactor microondas a 120°C durante 15 minutos. La mezcla de reacción se evaporó, y se agregó THF al residuo. La mezcla se filtró, y el eluyente se concentró. El residuo se recristalizó de THF y hexano para proporcionar el compuesto del título (0.19g, 74%). ^{1}H NMR (500MHz, THF): δ 1.53 (d, 6H), 2.62 (t, 2H), 3.16-3.20 (m, 2H), 4.30-4.38 (m, 1H), 6.38 (s, 1H), 6.63 (t, 1H), 6.87 (d, 2H), 7.48-7.51 (m, 3H), 7.56-7.58 (m, 2H), 7.68 (d, 2H); ^{13}C NMR (125MHz, THF): δ 19.4, 35.6, 44.7, 47.0, 106.9, 126.3, 126.5, 128.6, 128.8, 129.4, 132.0, 135.6, 142.3, 143.3, 158.5; Espectro de Masa: M+H^+ 450.

Ejemplo 116

4-{2-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

Una mezcla de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (0.15g, 0.52mmol), 4-(2-aminoetil)benzonitrilo (0.09g, 0.63mmol) y TEA (0.07g, 0.68mmol) en MeCN (1.5ml) se calentó en un reactor microondas a 120°C durante 35 minutos. Se agregó 4-(2-aminoetil)benzonitrilo (0.04g) a la mezcla de reacción, y se calentó en un reactor microondas a 120°C durante 20 minutos. La mezcla de reacción se evaporó, y el producto crudo se purificó por cromatografía rápida en columna usando hexano y EtOAc, 80:20- 50:50, como eluyente, para proporcionar el compuesto del título (0.14g, 67%). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.57 (d, 6H), 2.63 (t, 2H), 3.15-3.19 (m, 2H), 4.37-4.43 (m, 1H), 5.46 (brm, 1H), 6.86 (d, 2H), 7.45-5.55 (m, 7H); ^{13}C NMR (125MHz, $CDCl_3$): δ 20.4, 36.2, 44.5, 47.9, 107.8, 111.0, 118.9, 125.2, 129.1, 129.5, 130.1, 131.8, 132.7, 135.1, 143.1, 158.6; Espectro de Masa: M-H$^+$ 394.

Ejemplo 117

3-{2-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (150mg, 0.525mmol) se disolvió en DMF seco (1mL) bajo una atmósfera de nitrógeno. Se agregó 3-(2-aminoetil)benzonitrilo (78mg, 0.530mmol), seguido por TEA (53mg, 0.525mmol), y la mezcla de reacción se calentó en un reactor microondas a 120°C durante 20 minutos. La mezcla se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ acuoso saturado, se secó sobre Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó en un sistema HPFC Biotage Horizon usando heptano y EtOAc como eluyente proporcionando el compuesto del título (118mg, 56.3%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (d, 6H), 2.60 (t, 2H), 3.17 (q, 2H), 4.37-4.46 (m, 1H), 5.49 (bs, 1H), 6.88 (s, 1H), 7.02 (d, 1H), 7.30-7.34 (m, 1H), 7.47 -7.57 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.38, 35.75, 44.70, 47.90, 107.72,

113.00, 118.70, 125.17, 129.19, 129.67, 130.36, 130.77, 131.95, 132.20, 133.23, 135.11, 139.03, 158.60; Espectro de Masa: $M+H^+$ 396.1.

Ejemplo 118

1,1-Dióxido de 4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-il}amino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona (150mg, 0.525 mmol) se disolvió en DMF seco (1mL) bajo una atmósfera de nitrógeno. Se agregó 1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-amina (133mg, 0.530 mmol), seguido por TEA (53mg, 0.525mmol), y la mezcla de reacción se calentó en un reactor microondas a 120°C durante 20 minutos. La mezcla se diluyó con EtOAc, se lavó con $NaHCO_3$ acuoso saturado, se secó con Na_2SO_4, se filtró y se evaporó. El producto crudo se purificó en un sistema HPFC Biotage Horizon usando heptano y EtOAc como eluyente proporcionando el compuesto del título (223g, 84.0%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.60 (d, 6H), 4.01-4.06 (m, 3H), 4.10-4.15 (m, 2H), 4.40-4.48 (m, 1H), 5.62 (bs, 1H), 7.51 (s, 5H), 7.59 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.38, 44.61, 48.06, 59.87, 109.52, 115.56, 117.98 (q, J_{C-F}=33.6HZ), 124.42, 124.75, 129.29, 130.48, 131.49, 134.49, 135.16, 143.70, 156.92, 158.26; Espectro de Masa: $M+H^+$ 501.1.

Ejemplo 119

1,1-Dióxido de 2-*terc*-butil-4-[(2-{[3-cloro-5-(trifluorometil)piridin-2-il]amino}etil) amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-Dióxido de 4-[(2-aminoetil)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona (0.088g, 0.27mmol), 2,3-dicloro-5-(trifluorometil)piridina (0.065g, 0.30mmol) y TEA (0.055g, 0.54mmol) se disolvió en DMF seco (3 ml) y se calentó en un reactor microondas a 120 °C durante 25 minutos. La mezcla de reacción se extrajo con EtOAc (75 ml), y las fases orgánicas se lavaron con agua (3x50 ml), se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se purificó por cromatografía en columna en gel de sílice usando éter de petróleo y EtOAc (85:15) como eluyente, para producir el

compuesto del título (0.052g, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.3-8.25 (m, 1H), 7.67-7.62 (m, 2H), 7.49-7.43 (m, 2H), 7.43-7.35 (m, 3H), 6.47-6.41 (m, 1H), 5.47-5.41 (m, 1H), 3.52 (q, 2H), 3.09 (q, 2H), 1.7 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 155.7, 143.7, 143.6, 135.5, 133.2, 133.1, 131.5, 129.4, 128.5, 125, 124.6, 122.4, 116.8, 116.6, 115, 107.1, 61.4, 45.4, 40.9, 27.5; Espectro de Masa: M-H$^+$ 503.

Ejemplo 120

2-{2-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenil metanosulfonato

2-[(2-Isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] etil 4-metilbencenosulfonato (200mg, 0.431mmol) se disolvió en MeCN seco (4mL) bajo una atmósfera de nitrógeno. Se agregó 2-hidroxifenil metanosulfonato (89mg, 0.474mmol), seguido por carbonato de potasio (297mg, 2.152mmol). La mezcla de reacción se calentó en un reactor microondas durante 15 minutos a 120°C. Carbonato de potasio se filtró completamente, y la mezcla de reacción se concentró y se re-disolvió en EtOAc. La mezcla se lavó con $NaHCO_3$, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se purificó en un sistema Horizon TM flash usando heptano y EtOAc como eluyente y TEA como aditivo y, a continuación, se purificó por cromatografía en columna (ISOLUTE SI, (5g)) usando DCM como eluyente para proporcionar el compuesto del título (31mg, 15%). ^{1}H NMR ($CDCl_3$, 500MHz): δ 1.59 (d, 6H), 3.22 (s, 3H), 3.31 (q, 2H), 3.96 (t, 2H), 4.38-4.46 (m, 1H), 5.88 (t, 1H), 6.89 (d, 1H), 7.02 (t, 1H), 7.23-7.30 (m, 2H), 7.46-7.48 (m, 3H), 7.53-7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 20.38, 38.57, 43.36, 47.85, 67.23, 108.08, 114.71, 122.38, 124.59, 125.14, 128.55, 129.15, 130.09, 131.63, 135.62, 138.64, 150.55, 158.40; Espectro de Masa: M-H$^+$ 481.1.

Ejemplos 121 a 139 se prepararon de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y la amina apropiada en analogía con las descripciones para los Ejemplos 1, 4, 15, 23, 24, 49, 76-82, 84-88, 90-97. El material de partida o bien se encuentra disponible en el comercio o bien

puede prepararse como se describe o en analogía con métodos descritos en la sección para la Síntesis de Material de Partida e Intermedios, o pueden prepararse de acuerdo con métodos conocidos por la persona experta en el arte.

Ejemplo 121

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-({2-[2-(trifluorometoxi)fenil]etil} amino)isotiazol-3(2H)-ona

2-[2-(Trifluorometoxi)fenil]etanamina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.49-7.43 (m, 3H), 7.29-7.12 (m, 3H), 6.77-6.73 (m, 1H), 5.40-5.33 (m, 1H), 3.19-3.11 (m, 2H), 2.72-2.65 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.6, 147.8, 134.8, 131.7, 130.9, 130.0, 129.8, 128.8, 128.5, 127.0, 125.1, 120.7, 107.7, 61.6, 43.6, 30.1, 27.7; Espectro de Masa: M-H^+ 469.

Ejèmplo 122

1,1-Dióxido de 4-[(1-bencilpirrolidin-3-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1-Bencilpirrolidin-3-amina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR(500MHZ $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.46-7.40 (m, 3H), 7.35-7.30 (m, 2H), 7.30-7.24 (m, 3H), 5.53 (d, 1H), 3.68-3.60 (m, 1H), 3.52 (dd, 2H), 2.74-2.68 (m, 1H), 2.45 (dd, 1H), 2.30-2.22 (m, 1H), 2.22-2.14 (m, 1H), 1.80-1.64 (m, 10H), 1.60-1.52 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 138.5, 134.5, 131.9, 129.8, 128.9, 128.6, 127.4, 125.2, 107.1, 61.7, 60.8, 59.9, 52.7, 52.4, 33.1, 27.8; Espectro de Masa: M+H^+ 440.

Ejemplo 123

N -Bencil-N^2-(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinamida

N^1-Bencilglicinamida se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.48-7.22 (m, 10H), 6.04-5.97 (m, 1H), 5.78-5.71 (m, 1H), 4.39 (d, 2H), 3.52 (d, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):5 166.9, 159.2, 137.4, 134.9, 131.4, 130.0, 129.0, 128.9, 128.2, 128.1, 124.5, 109.7, 61.8, 46.7, 43.9, 41.0, 27.7; Espectro de Masa: M-H^+ 428.

Ejemplo 124

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(2-piridin-2-iletil)amino]isotiazol-3(2*H*)-ona

2-Piridin-2-iletanamina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}HNMR (500 MHz, $CDCl_3$):δ 8.57-8.50 (m, 1H), 7.61-7.48 (m, 3H), 7.47-7.38 (m, 3H), 7.18-7.10 (m, 1H), 6.95-6.88 (m, 1H), 6.32-6.22 (m, 1H), 3.30-3.21 (m, 2H), 2.84-2.77 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.7, 158.3, 149.5, 136.8, 135.3, 131.6, 129.5, 128.7, 125.4, 123.3, 121.9, 106.8, 61.4, 43.4, 36.7, 27.7; Espectro de Masa: M-H^+ 386.

Ejemplo 125

1,1-Dióxido de 2-*terc*-butil-4-{[2-(2-clorofenil)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

2-(2-Clorofenil)etanamina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.55-7.49 (m, 2H), 7.49-7.43 (m, 3H), 7.34-7.30 (m, 1H), 7.20-7.10 (m, 2H), 6.78-6.74 (m, 1H), 5.42-5.35 (m, 1H), 3.23-3.15 (m, 2H), 2.79-2.71 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.7, 135.3, 134.9, 134.1, 131.6, 130.8, 129.8, 129.8, 128.8, 128.5, 127.1, 125.2, 107.6, 61.6, 43.3, 41.0, 33.7, 27.7; Espectro de Masa: M-H^+ 419.

Ejemplo 126

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-({2-[3-(trifluorometil)fenil]etil} amino)isotiazol-3(2*H*)-ona

2-[3-(Trifluorometil)fenil]etanamina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.40 (m, 6H), 7.33- 7.27 (m, 1H), 6.98-6.93 (m, 1H), 6.91-6.88 (m, 1H), 5.62-5.55 (m, 1H), 3.16-3.10 (m, 2H), 2.62-2.56 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.8, 138.6, 134.9, 132.2, 131.9, 131.2, 130.9, 130.2, 130.0, 129.2, 129.0, 125.4, 125.4, 125.2, 123.8, 123.8, 123.1, 107.5, 61.8, 44.8, 41.1, 36.0, 27.8; Espectro de Masa: M-H^+ 453.

Ejemplo 127

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(4-{[4-(trifluorometil)fenil]tio} ciclohexil)amino] isotiazol-3(2H)-ona

4-{[4-(Trifluorometil)fenil]tio}ciclohexanamina se utilizó asimismo como material de partida para producir el compuesto del título como una mezcla de cis y trans isómeros. ^{1}H NMR (500MHz, $CDCl_3$): 60.87-0.95 (m, 2H), 1.12-1.20 (m, 2H), 1.42-1.92 (m, 30H), 2.00 (s, 2H), 2.88-3.09 (m, 3H), 3.37-3.40 (m, 1H), 5.15 (d, 1H), 5.31 (d, 1H), 7.35-7.38 (m, 4H), 7.42-7.52 (m, 14H); ^{13}C NMR (125MHz, $CDCl_3$): δ 27.83, 28.65, 31.43, 33.02, 43.22, 44.30, 50.35, 51.25, 61.79, 106.92, 124.28 (q, J(C-F)=272.2Hz), 125.26, 125.44, 125.97, 128.84, 128.90, 129.94, 130.13, 130.18, 130.57, 131.85, 131.89, 134.09, 134.19, 140.20, 140.67, 159.96; Espectro de Masa: M- H^+ 536.9.

Ejemplo 128

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-({1-[5-(trifluorometil)piridin-2-il]piperidin-4-il} amino)isotiazol-3(2*H*)-ona

1-[5-(Trifluorometil)piridin-2-il]piperidin-4-amina se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.38-8.32 (m, 1H), 7.63-7.51 (m, 3H), 7.51-7.43 (m, 3H), 6.62-6.54 (m, 1H), 5.21 (d, 1H), 4.21-4.14 (m, 2H), 3.25-3.15 (m, 1H), 2.60-2.50 (m, 2H), 1.82-1.70 (m, 2H), 1.74 (s, 9H), 1.4-1.29 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.7, 145.6, 134.8, 134.0, 131.8, 130.1, 128.9,

125.2, 107.4, 105.9, 61.8, 50.3, 43.5, 31.9, 27.7; Espectro de Masa: M-H^+ 509.

Ejemplo 129

***terc*-Butil 3-{2-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etoxi}azetidin-1-carboxilato**

terc-Butil 3-(2-aminoetoxi)azetidin-1-carboxilato se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.53-7.48 (m, 2H), 7.47-7.42 (m, 3H), 5.57-5.51 (m, 1H), 4.16-4.10 (m, 1H), 4.07-4.00 (m, 2H), 3.80-3.74 (m, 2H), 3.31-3.26 (m, 2H), 3.06-3.00 (m, 2H), 1.74 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$): δ 159.6, 156.3, 135.1, 131.6, 129.8, 128.8, 125.0, 107.9, 79.8, 68.2, 66.5, 61.7, 56.4, 43.6, 28.5, 27.7; Espectro de Masa: M-H^+ 480.

Ejemplo 130

1,1-Dióxido de 2-*terc*-butil-4-[(2,2-dimetilpropil)amino]-5-fenilisotiazol-3(2*H*)-ona

2,2-Dimetilpropan-1-amina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.46 (m, 2H), 7.46-7.41 (m, 3H), 5.34-5.26 (m, 1H), 2.62 (d, 2H), 1.75 (s, 9H), 0.81 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$):δ 159.9, 135.5, 131.8, 129.6, 128.7, 125.3, 106.6, 61.6, 55.3, 31.9, 27.7, 27.0; Espectro de Masa: M-H^+ 351.

Ejemplo 131

Metil ({[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4- il) amino]acetil}amino)acetato

Glicilglicinato de metilo, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.54-7.48 (m, 2H), 7.48-7.44 (m, 3H), 6.03 (t, 1H), 5.98 (t, 1H), 4.00 (d, 2H), 3.78 (s, 3H), 3.56 (d, 2H), 1.74 (s, 9H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 170.1, 167.5, 159.3, 134.9, 131.6, 130.2, 129.1, 124.5, 109.9, 61.9, 52.8, 46.7, 41.4, 27.8; Espectro de Masa: $M+H^+$410.

Ejemplo 132

1,1-Dióxido de 2-*terc*-butil-4-[(1-metilpiperidin-4-il)amino]-5-fenilisotiazol-3(2*H*)-ona

1-Metilpiperidin-4-amina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500 MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.50-7.42 (m, 3H), 5.19 (d, 1H), 2.96-2.86 (m, 1H), 2.63-2.58 (m, 2H), 2.15 (s, 3H), 1.74 (s, 9H), 1.68-1.52 (m, 4H), 1.44-1.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 134.3, 131.9, 129.9, 128.9, 125.4, 106.8, 61.8, 54.1, 49.8, 46.2, 32.6, 27.8; Espectro de Masa: $M+H^+$ 378.

Ejemplo 133

1,1-Dióxido de 2-*terc*-butil-4-{[(5-metil-3-fenilisoxazol-4-il)metil] amino}-5-fenilisotiazol- 3(2*H*)-ona

l-(5-Metil-3-fenilisoxazol-4-il)metanamina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500 MHz, $CDCl_3$): δ 7.53-7.46 (m, 7H), 7.43-7.38 (m, 3H), 5.08 (t, 1H), 3.86 (d, 2H), 2.32 (s, 3H), 1.71 (s, 9).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 162.2, 159.2, 134.5, 131.4, 130.2, 130.1, 129.3, 128.9, 128.7, 128.1, 124.9, 109.6, 109.4, 61.9, 37.8, 27.8, 11.4; Espectro de Masa: $M+H^+$452.

Ejemplo 134

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[(1,3,5-trimetil-1H-pirazol-4-il) metil]amino} isotiazol-3(2*H*)-ona

1-(1,3,5-Trimetil-1H-pirazol-4-il)metanamina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500 MHz, $CDCl_3$): δ 7.61-7.56 (m, 2H), 7.49-7.43 (m, 3H), 4.96 (t, 1H), 3.68 (s, 5H), 2.11 (s, 3H), 2.07 (s, 3H), 1.73 (s, 9H); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 159.6, 146.3, 137.9, 134.9, 131.8, 129.8, 128.8, 125.4, 111.8, 107.8, 61.8, 38.8, 36.1, 27.8, 11.8, 9.8.; Espectro de Masa: $M+H^+$403.

Ejemplo 135

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(2-{[5-(trifluorometil)piridin-2-il] oxi}etil) amino] isotiazol-3(2*H*)-ona

2-{[5-(Trifluorometil)piridin-2-il]oxi}etanamina se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500 MHz, $CDCl_3$): δ 8.43-8.39 (m, 1H), 7.83-7.78 (m, 1H), 7.54-7.48 (m, 2H), 7.47-7.40 (m, 3H), 6.87-6.81 (m, 1H), 5.93 (brs, 1H), 4.37-4.32 (m, 2H), 3.29-3.23 (m, 2H), 1.73 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 159.7, 145.0, 145.0, 136.4, 136.3, 135.3, 131.7, 129.9, 129.0, 125.1, 123.0, 121.1, 120.8, 111.6, 108.0, 64.7, 61.8, 43.8, 27.8; Espectro de Masa: $M+H^+$ 470.

Ejemplo 136

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-({2-[4-(trifluorometoxi)fenil]etil} amino)isotiazol-3(2*H*)-ona

2-[4-(Trifluorometoxi)fenil]etanamina se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.49-7.41 (m, 3H), 7.07-7.02 (m, 2H), 6.80-6.75 (m, 2H), 5.48-5.42 (m, 1H), 3.14-3.06 (m, 2H), 2.59-2.52 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 148.2, 136.4, 135.0, 131.9, 130.0, 130.0, 129.0, 125.3, 121.4, 107.6, 61.8, 45.0, 41.1, 35.4, 27.8; Espectro de Masa: $M+H^+$ 469.

Ejemplo 137

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-[(2,2,2-trifluoroetil)amino]isotiazol-3(2*H*)-ona

2,2,2-Trifluoroetanamina, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR

(500 MHz, $CDCl_3$): δ 7.52-7.45 (m, 5H), 5.42-5.36 (m, 1H), 3.52-3.45 (m, 2H), 1.73 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 133.8, 131.3, 130.5, 129.2, 124.5, 123.5, 122.3, 111.0, 61.9, 44.8, 44.5, 44.3, 44.0, 27.5; Espectro de Masa: $M+H^+$ 363.

Ejemplo 138

1,1-Dióxido de 2-*terc*-butil-4-[(2,3-dihidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

3-Aminopropano-1,2-diol, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51-7.45 (m, 2H), 7.45-7.40 (m, 3H), 5.75 (brs, 1H), 3.65-3.58 (m, 1H), 3.43-3.36 (m, 1H), 3.32-3.24 (m, 1H), 3.02-2.85 (m, 2H), 2.11 (brs, 2H), 1.72 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 135.5, 131.8, 130.0, 129.0, 125.1, 107.7, 70.2, 64.3, 61.9, 46.3, 27.8; Espectro de Masa: $M+H^+$ 355. 5

Ejemplo 139

3-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] propanenitrilo

^1H NMR (500 MHz, $CDCl_3$): δ 7.52-7.42 (m, 5H), 5.63-5.56 (m, 1H), 3.22-3.13 (m, 2H), 2.25-2.17 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 134.5, 131.6, 130.6, 129.3, 124.4, 117.1, 109.4, 62.1, 39.5, 27.8, 18.5; Espectro de Masa: $M+H^+$ 334. 3-Aminopropanenitrilo, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título.

Ejemplos 140 a 143 se prepararon de 2-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-5 dihidroisotiazol-4-il)amino]etil 4-metilbencenosulfonato y el fenol apropiado o tiofenol en analogía con las descripciones para Ejemplo 99 y 101-103. El material de partida o bien se encuentra disponible en el comercio o bien puede prepararse como se describe o en analogía con métodos descritos en la sección para la Síntesis de Material de Partida e

Intermedios, o pueden prepararse de acuerdo con métodos conocidos por la persona experta en el arte.

Ejemplo 140

1,1-Dióxido de 2-*terc*-butil-5-fenil-4- [(2-{[3-(trifluorometoxi)fenil]tio} etil)amino]isotiazol-3(2*H*)-ona

3-(Trifluorometoxi)bencenotiol, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.73 (s, 9H), 2.84 (t, 2H), 3.10 (q, 2H), 5.59 (bs, 1H), 7.07-7.09 (m, 2H), 7.14 (d, 1H), 7.30 (t, 1H), 7.38-7.46 (m, 5H); ^{13}C NMR (125MHz, $CDCl_3$): δ 27.82, 33.62, 42.54, 61.86, 108.39, 119.41, 120.59 (q, J=258.1Hz), 122.37, 124.90, 128.26, 128.99, 130.05, 130.57, 131.53, 134.81, 136.94, 149.74, 159.59; Espectro de Masa: $M+NH4^+$ 517.7.

Ejemplo 141

1,1-Dióxido de 2-*terc*-butil-4-{[2-(4-clorofenoxi)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

4-Clorofenol, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500MHz $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.50-7.42 (m, 3H), 7.24 (d, 2H), 6.76 (d, 2H), 5.62 (t, 1H), 3.84 (t, 2H), 3.28-3.22 (m, 2H), 1.74 (s, 9H); ^{13}C NMR (125MHz $CDCl_3$): 159.6, 156.9, 135.2, 131.7, 130.0, 129.7, 129.0, 126.7, 125.1, 115.9, 108.3, 66.3, 61.9, 43.4, 27.8; Espectro de Masa: $M+H^+$ 435.

Ejemplo 142

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-({2-[3-(trifluorometoxi)fenoxi]etil} amino)isotiazol-3(2*H*)-ona

3-(Trifluorometoxi)fenol, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^{1}H NMR (500MHz, $CDCl_3$): δ 1.75 (s, 9H), 3.27 (q, 2H), 3.87 (t, 2H), 5.63 (t, 1H), 6.70 (s, 1H), 6.77 (m, 1H), 6.86 (m, 1H), 7.28-7.31 (m, 1H), 7.46-7.48 (m, 3H), 7.53-7.55 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 27.84, 43.28, 61.88,

66.34, 107.90, 108.41, 113.03, 113.92, 120.64 (q, J=256.2Hz), 125.06, 129.06, 130.07, 130.61, 131.70, 135.14, 150.36, 159.29, 159.65; Espectro de Masa: $M+NH4^+$ 501.8.

Ejemplo 143

1,1-Dióxido de 4-{[2-(bifenil-2-iltio)etil]amino}-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

Bisfenil-2-tiol, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR ($CDCl_3$, 500MHz): δ 1.72 (s, 9H), 2.56 (t, 2H), 2.87 (q, 2H), 5.39 (bs, 1H), 7.26-7.44 (m, 14H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 27.84, 33.78, 42.49, 61.67, 107.71, 125.02, 127.42, 127.78, 128.34, 128.88, 129.61, 129.84, 130.94, 131.25, 131.57, 132.58, 134.86, 140.70, 144.20, 159.46; Espectro de Masa: $M+H^+$ 492.9.

Ejemplos 144 y 145 se prepararon de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) y el haluro de acilo apropiado en analogía con las descripciones para Ejemplo 105, 111 y 112. El material de partida o bien se encuentra disponible en el comercio o bien puede prepararse como se describe, o en analogía con métodos descritos en la sección para la Síntesis de Material de Partida e Intermedios, o pueden prepararse de acuerdo con métodos conocidos por la persona experta en el arte.

Ejemplo 144

1,1-Dióxido de 4-[(1-acetilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2H)-ona

Cloruro de acetilo, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500MHz $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.49-7.43 (m, 3H), 5.20 (d, 1H), 4.39-4.33 (d, 1H), 3.63-3.57 (m, 1H), 3.16-3.08 (m, 1H), 2.58 (ddd, 1H), 2.24 (ddd, 1H), 1.86-1.64 (m, 11H), 1.28-1.19 (m, 2H); ^{13}C NMR (125MHz

$CDCl_3$): δ 169.0, 159.7, 133.9, 131.9, 130.2, 128.9, 125.2, 107.6, 61.9, 50.3, 44.8, 40.1, 32.9, 32.1, 27.8, 21.6; Espectro de Masa: $M\text{-}H^+$ 404

Ejemplo 145

1,1-Dióxido de 2-*terc*-butil-4-[(1-isobutirilpiperidin-4-il)amino]-5-fenilisotiazol-3(2*H*)-ona

Cloruro de 2-metilpropanoilo, disponible en el comercio, se utilizó asimismo como material de partida para producir el compuesto del título. ^1H NMR (500MHz $CDCl_3$): δ 7.56-7.50 (m, 2H), 7.44-7.40 (m, 3H), 5.18 (d, 1H), 4.42-4.27 (m, 2H), 3.79-3.74 (m, 1H), 3.19-3.09 (m, 1H), 2.69 (sp, 1H), 2.62-2.52 (m, 1H), 2.30-2.20 (m, 1H), 1.78-1.66 (m, HH), 1.29-1.17 (m, 2H), 1.12-1.02 (m, 6H); ^{13}C NMR (125MHz $CDCl_3$): 175.5, 159.8, 133.9, 131.8, 130.2, 128.9, 125.3, 107.5, 61.9, 50.4, 43.7, 40.3, 33.2, 32.2, 30.2, 27.8, 19.7, 19.5; Espectro de Masa: $M\text{-}H^+$ 432.

Ejemplo 146

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[1-(2-feniletil)piperidin-4-il] amino}isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75) y (2-bromoetil)benceno en una manera similar como se describe para Ejemplo 104. ^1H NMR (500MHz $CDCl_3$): δ 7.64-7.50 (m, 2H), 7.48-7.45 (m, 3H), 7.30-7.25 (m, 2H), 7.22-7.17 (m, 1H), 7.16-7.12 (m, 2H), 5.22 (d, 1H), 3.00-2.90 (m, 1H), 2.81-2.74 (m, 2H), 2.73-2.67 (m, 2H), 2.50-2.43 (m, 2H), 1.82-1.60 (m, 13H), 1.46-1.36 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.9, 140.2, 134.3, 131.9, 130.0, 128.9, 128.6, 126.3, 125.4, 106.9, 61.8, 60.2, 51.8, 50.2, 33.8, 32.4, 27.9; Espectro de Masa: $M+H^+$ 468

Ejemplo 147

1,1-Dióxido de 2-*terc*-butil-5-fenil-4-{[2-(pirrolidin-3-iltio)etil]amino} isotiazol-3(2*H*)-ona

El compuesto del título se preparó de Ejemplo 100 en analogía con la descripción de 1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3(2*H*)-ona (Ejemplo 75). ^{1}H NMR (500MHz, $CDCl_3$): δ 1.68-1.75 (m, 10H), 1.98 (s, 4H), 2.12-2.19 (m, 1H), 2.49 (t, 2H), 2.83-2.86 (m, 1H), 3.06-3.14 (m, 4H), 3.20-3.25 (m, 1H), 3.31-3.35 (m, 1H), 5.71 (t, 1H), 7.44-7.46 (m, 3H), 7.50-7.52 (m, 2H), 8.02 (bs, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 23.12, 27.82, 31.51, 32.59, 41.96, 43.05, 44.42, 51.25, 61.87, 108.12, 125.11, 129.06, 130.08, 131.65, 134.85, 159.64; Espectro de Masa: $M+H^+$ 410.1.

Ejemplo 148

1,1-Dióxido de 2-*terc*-butil-4-{[(5-metilisoxazol-3-il)metil]-amino}-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó como se describe para Ejemplo 24 de 1 equivalente de [(5-metilisoxazol-3-il)metil]-amina, 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 1 equivalente de TEA con un timepo de reacción de 45 minutos. La mezcla se evaporó y se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 35% EtOAc en pentano como eluyente para producir el compuesto del título (0.070g, 56%). ^{1}HNMR (500MHz $CDCl_3$): δ 7.52-7.48 (m, 2H), 7.46-7.41 (m, 3H), 5.73 (s, 1H), 5.66 (t, 1H), 5.07 (d, 2H), 2.39 (s, 3H), 1.74 (s, 9H); ^{13}C NMR (125MHz CDCl3): δ 170.7, 159.9, 159.4, 134.8, 131.6, 130.1, 128.9, 124.7, 109.3, 100.4, 61.9, 40.4, 27.8, 12.5; Espectro de Masa: $M+H^+$ 376

Ejemplo 149

1,1-Dióxido de 4-{[2-(3,4-dimetoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y [2-(3,4-dimetoxifenil)etil]amina en una manera similar como se describe para Ejemplo 24. ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.52 (m, 2H), 7.50-7.46 (m, 3H), 6.76 (d, 1H), 6.46 (dd, 1H), 6.36 (d,

1H), 5.40 (t, 1H), 4.41 (sept, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.13 (q, 2H), 2.57 (t, 2H), 1.59 (d, 6H); ^{13}C NMR (125MHz, CDCl3): δ 158.7, 149.3, 148.1, 135.4, 131.7, 130.0, 129.9, 128.8, 125.4, 120.8, 111.8, 111.7, 107.2, 56.1, 47.8, 45.3, 35.6, 20.3; Espectro de Masa M+H$^+$ 431

Ejemplo 150

1,1-Dióxido de 4-{[2-(3-cloro-4-metoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y [2-(3-cloro-4-metoxifenil)etil]amina en una manera similar como se describe para Ejemplo 24. ^{1}H NMR (500MHz DMSO-d_6): δ 7.55-7.47 (m, 5H), 7.34 (t, 1H), 6.94 (d, 1H), 6.65 (dd, 1H), 6.61 (d, 1H), 4.32 (qt, 1H), 3.78 (s, 3H), 3.03-2.96 (m, 2H), 2.43-2.37 (m, 2H), 1.46 (d, 6H); ^{13}C NMR (125MHz DMSOd_6): δ 158.7, 153.7, 136.1, 132.4, 131.9, 130.3, 129.4, 128.8, 126.1, 121.3, 113.3, 105.0, 56.7, 47.3, 45.0, 34.4, 20.5; Espectro de Masa M+H$^+$ 435

Ejemplo 151

4-{2-[(2-Isobutil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenil metanosulfonato

Una mezcla de 4-{2-[1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenil metanosulfonato (0.096g, 0.227mmol), 1-bromo-2-metilpropano (0.050g, 0.364mmol)) y TEA (0.041ml, 0.295mmol) en DMSO se calentó en un microondas a 100°C durante 40 minutos y a 130°C durante 1 hora. La mezcla de reacción se evaporó a sequedad, y el residuo se purificó por cromatografía en columna en gel de sílice (Horizons Biotage) usando 15- 100% EtOAc en pentano como eluyente para producir el compuesto del título (0.047 g, 43%) como un sólido; ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.46 (m, 5H), 7.15 (d, 2H), 6.84 (d, 2H), 5.43 (t, 1H), 3.52 (d, 2H), 3.21-3.15 (m, 2H), 3.14 (s, 3H), 2.64-2.58 (m, 2H), 2.32-2.23 (m, 1H), 1.02 (d, 6H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.6, 148.2, 136.9,

135.2, 131.8, 130.3, 130.2, 129.1, 125.2, 122.5, 107.8, 47.9, 44.9, 37.6, 35.5, 27.8, 20.3; Espectro de Masa: $M+H^+$ 479

Ejemplo 152

1,1-Dióxido de 2-isopropil-5-fenil-4-[(1-piridin-2-ilpiperidin-4-il)amino] isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y diclorhidrato de 1-piridin-2-ilpiperidin-4-amina en una manera similar como se describe para Ejemplo 24 con TEA como base. ^1H NMR (500MHz $CDCl_3$): δ 8.14 (dd, 1H), 7.58-7.53 (m, 2H), 7.48-7.41 (m, 4H), 6.62-6.55 (m, 2H), 5.23 (d, 1H), 4.42 (sept, 1H), 4.10- 4.02 (m, 2H), 3.22-3.12 (m, 1H), 2.49-2.41 (m, 2H), 1.80-1.72 (m, 2H), 1.59 (d, 6H), 1.42- 1.33 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): 159.2, 158.7, 148.1, 137.7, 134.5, 131.9, 130.2, 128.9, 125.3, 113.6, 107.5, 106.9, 50.8, 47.8, 44.1, 32.1, 20.4; Espectro de Masa: $M+H^+$ 427

Ejemplo 153

4-(2-{[2-(4-Fluorobencil)-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il]amino}etil)fenil metanosulfonato

El compuesto del título se preparó de 4-{2-[1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}fenil metanosulfonato y 1-(bromometil)-4-fluorobenceno en una manera similar como se describe para Ejemplo 151. ^1H NMR (500MHz $CDCl_3$): δ 7.56-7.46 (m, 7H), 7.14 (d, 2H), 7.06 (t, 2H), 6.83 (d, 2H), 5.39 (t, 1H), 4.80 (s, 2H), 3.19- 3.14 (m, 2H), 3.13 (s, 3H), 2.61 (t, 2h); ^{13}C NMR (125MHz $CDCl_3$): 163.9, 161.9, 159.0, 148.2, 136.8, 135.2, 131.8, 131.1, 131.0, 130.3, 129.2, 124.9, 122.5, 115.9, 115.7, 107.9, 44.9, 43.1, 37.7, 35.5; Espectro de Masa: $M+H^+$ 531

Ejemplo 154

1,1-Dióxido de 2-isopropil-4-(isopropilamino)-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona e isopropilamina en una manera similar como se

describe para Ejemplo 24. ^{1}H NMR (500MHz $CDCl_3$): δ 7.56-7.51 (m, 2H), 7.48-7.43 (m, 3H), 5.14 (d, 1H), 4.42 (sept, 1H), 3.40-3.30 (m, 1H), 1.60 (d, 6H), 1.00 (d, 6H); ^{13}C NMR (125MHz $CDCl_3$): δ 158.9, 134.6, 131.7, 129.9, 128.9, 125.5, 106.3, 47.8, 44.9, 23.0, 20.4; Espectro de Masa: $M+H^+$ 309.

Ejemplo 155

1,1-Dióxido de 2-isopropil-5-fenil-4-[(1-piridin-2-ilazetidin-3-il)amino] isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y 1-piridin-2-ilazetidin-3-amina en una manera similar como se describe para Ejemplo 118. ^{1}HNMR (500MHz $CDCl_3$): δ 1.57 (d, 6H), 3.71-3.75 (m, 2H), 3.84 (t, 2H), 4.04-4.10 (m, 1H), 4.37-4.45 (m, 1H), 5.71-5.76 (m, 1H), 6.19 (d, 1H), 6.60-6.64 (m, 1H), 7.40-7.44 (m, 1H), 7.46-7.52 (m, 5H), 8.10-8.12 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 20.36, 44.88, 48.00, 58.15, 106.25, 109.08, 113.90, 124.58, 129.24, 130.35, 131.46, 134.60, 137.46, 148.39, 10 158.35, 160.10; Espectro de Masa: $M+H^+$ 399.

Ejemplo 156

1,1-Dióxido de 4-{[2-(4-hidroxi-3,5-dimetoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y 4-(2-aminoetil)-2,6-dimetoxifenol en una manera similar como se describe para Ejemplo 118. ^{1}H NMR (THF-d_8, 500MHz): δ 1.53 (d, 6H), 2.45 (t, 2H), 3.11 (q, 2H), 3.73 (s, 6H), 4.31-4.39 (m, 1H), 6.03 (s, 2H), 6.47 (t, 1H), 7.22 (s, 1H), 7.46-7.50 (m, 3H), 7.55-7.57 (m, 2H); ^{13}C NMR (125MHz, THF-d8): δ 19.57, 35.92, 45.47, 46.98, 55.93, 106.13, 106.56, 126.64, 127.87, 128.56, 129.34, 131.86, 135.49, 135.64, 148.12, 158.61; Espectro de Masa: $M+H^+$ 447.

Ejemplo 157

1,1-Dióxido de 4-{[2-(2-aminopiridin-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó en dos pasos. *terc*-Butil (4-{2-[(2-isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil} piridin-2-il)carbamato se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y *terc*-butil [4-(2-aminoetil) piridin-2-il]carbamato en una manera similar como se describe para Ejemplo 118. La desprotección de *terc*-butil (4-{2-[(2-isopropil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}piridin-2-il)carbamato, en una manera similar como se describe para 1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-amina, produjo el compuesto del título.

Ejemplo 158

1,1-Dióxido de 2-isopropil-5-fenil-4-[(2-piridin-4-iletil)amino]isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y (2-piridin-4-iletil)amina en una manera similar como se describe para Ejemplo 118. ^{1}H NMR (500MHz $CDCl_3$): δ 1.59 (d, 6H), 2.58 (t, 2H), 3.18 (q, 2H), 4.37-4.45 (m, 1H), 5.44 (t, 1H), 6.71-6.73 (m, 2H), 7.46-7.57 (m, 5H), 8.44-8.46 (m, 2H); ^{13}C NMR (125MHz $CDCl_3$): δ 20.37, 35.42, 44.14, 47.90, 107.90, 123.96, 125.15, 129.14, 130.19, 131.83, 135.12, 146.48, 150.27, 158.57; Espectro de Masa: $M+H^+$ 372.

Ejemplo 159

1,1-Dióxido de 2-isopropil-5-fenil-4-[(2-piridin-3-iletil)amino]isotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y (2-piridin-3-iletil)amina en una manera similar como se describe para Ejemplo 118. ^{1}HNMR (500MHz $CDCl_3$): δ 1.59 (d, 6H), 2.59 (t, 2H), 3.17 (q, 2H), 4.37-4.45 (m, 1H), 5.47 (t, 1H), 7.06-7.09

(m, 1H), 7.14-7.17 (m, 1H), 7.46-7.55 (m, 5H), 8.07 (s, 1H), 8.44-8.46 (m, 1H); ^{13}C NMR (125MHz $CDCl_3$): δ 20.38, 33.39, 44.78, 47.88, 107.76, 123.70, 125.15, 129.13, 130.20, 131.84, 133.02, 135.16, 136.13, 148.57, 150.06, 158.61; Espectro de Masa: $M+H^+$ 372.

Ejemplo 160

4-[2-({2-[(Metiltio)metil]-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il}amino)etil]fenil metanosulfonato

El compuesto del título se preparó de 4-{2-[1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}fenil metanosulfonato y 1,1,1-trifluoro-2-yodoetano en una manera similar como se describe para Ejemplo 151; ^{1}H NMR (500MHz $CDCl_3$): δ 7.58-7.48 (m, 5H), 7.16 (d, 1H), 6.85 (d, 2H), 5.41 (t, 1H), 4.77 (s, 2H), 3.21-3.15 (m, 1H), 3.14 (s, 3H), 2.63 (t, 2H), 2.38 (s, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 159.1, 148.2, 136.8, 135.2, 131.8, 130.4, 130.3, 129.2, 124.8, 122.5, 108.2, 45.0, 44.5, 37.7, 35.5, 16.8; Espectro de Masa: $M+H^+$ 483.

Ejemplo 161

1,1-Dióxido de 4-{[2-(3,5-dimetilisoxazol-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y [2-(3,5-dimetilisoxazol-4-il)etil]amina en una manera similar como se describe para Ejemplo 24. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.49-7.45 (m, 3H), 5.32 (t, 1H), 4.47 (sept, 1H), 3.04 (q, 2H), 2.33 (t, 2H), 2.14 (s, 3H), 2.01 (s, 3H), 1.59 (d, 6H); ^{13}C NMR (125MHz, $CDCl_3$): δ 166.1, 159.4, 158.6, 134.9, 131.4, 130.2, 129.2, 125.1, 109.7, 107.9, 47.9, 43.3, 23.0, 20.4, 11.1, 10.2; Espectro de Masa: $M+H^+$ 390

Ejemplo 162

1,1-Dióxido de 4-{[2-(3,5-dimetil-1H-pirazol-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

El compuesto del título se preparó de 1,1-dióxido de 4-cloro-2-isopropil-5-fenilisotiazol-3(2*H*)-ona y diclorhidrato de [2-(3,5-dimetil-1H-pirazol-4-il) etil]amina en una manera similar como se describe para Ejemplo 24 con TEA como base. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.53- 7.48 (m, 2H), 7.47-7.43 (m, 3H), 5.34 (t, 1H), 4.41 (sept, 1H), 3.01 (q, 2H), 2.41 (t, 2H), 2.05 (s, 6H), 1.58 (d, 6H); ^{13}C NMR (125MHz $CDCl_3$): δ 158.8, 135.3, 131.5, 129.9, 129.0, 125.3, 111.2, 107.2, 47.8, 43.9, 23.7, 20.4, 10.9; Espectro de Masa: $M+H^+$ 389

Ejemplo 163

4-[2-({2-[(5-Metilisoxazol-3-il)metil]-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il}amino)etil]fenil metanosulfonato

El compuesto del título se preparó de 4-{2-[l,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}fenil metanosulfonato y 3-(bromometil)-5-metilisoxazol en una manera similar como se describe para Ejemplo 151; ^{1}H NMR (500MHz $CDCl_3$): δ 7.57-7.46 (m, 5H), 7.13 (d, 2H), 6.82 (d, 2H), 6.16 (s, 1H), 5.43 (t, 1H), 4.87 (s, 2H), 3.22-3.08 (m, 5H), 2.61 (t, 3H), 2.41 (s, 3H); ^{13}C NMR (125MHz $CDCl_3$): δ 170.8, 158.9, 158.6, 148.2, 136.8, 135.2, 131.8, 130.4, 130.3, 129.2, 124.7, 122.5, 108.1, 101.8, 45.0, 37.7, 35.5, 35.1; Espectro de Masa: $M+H^+$ 518

Ejemplo 164

2,6-Dimetilfenil 4-[(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]butanoato

Clorhidrato de 2,6-dimetilfenil 4-aminobutanoato (80.4 mg, 0.33 mmol) y 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona (89.9 mg, 0.91 mmol) se disolvieron en una mezcla de MeCN/DMF (4:1, 5 ml, seco). TEA (0.134 ml) se agregó, y la mezcla de reacción se agitó a temperatura de la sala durante 15 horas. Se agregó éter dietílico (30 ml), y la mezcla resultante se extrajo con agua (2x 10 ml). La capa orgánica se secó ($MgSO_4$), se evaporó, y el residuo se purificó por cromatografía en columna en sílice, usando n-heptano/EtOAc (7:3) como eluyente. El producto

obtenido se purificó posteriormente por re-cromatografía, usando las condiciones ya indicadas, para producir el compuesto del título (17 mg, 11%) como un aceite incoloro, el cual se solidificó después de reposar. ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.73 (s, 9H), 1.78-1.85 (m, 2H), 2.06 (s, 6H), 2.38 (t, 2H), 2.96-3.01 (m, 2H), 5.37 (bt, 1H), 7.04 (s, 3H), 7.42-7.44 (m, 3H), 7.50- 7.52 (m, 2H).

Ejemplo 165

2-Mesitiletil N-(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato

El compuesto del título se preparó de ácido [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]acético y clorhidrato de metil glicinato. Espectro de Masa: $[M+H]^+$ 485.21, $[M-H]^-$ 483.28.

Ejemplo 166

2-[(2-*terc*-Butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil (2,6-dimetilfenil)acetato

El compuesto del título se preparó de Ejemplo 76 y ácido (2,6-dimetilfenil)acético. Espectro de Masa: $[M+H]^+$ 471.21, $[M-H]^-$ 469.34.

Ejemplo 167

Fenil N-(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato

El compuesto del título se preparó de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y clorhidrato de fenil β-alaninato en una manera similar como se describe para Ejemplo 164. Espectro de Masa: $[M+H]^+$ 429.11, $[M-H]^-$ 427.14.

Ejemplo 168

4-(Trifluorometoxi)fenil N-(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato

El compuesto del título se preparó de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y 4-(trifluorometoxi)fenil β-alaninato en una manera similar como se describe para Ejemplo 164. Espectro de Masa: $[M+H]^+$ 513.12, $[M-H]^-$ 511.16.

Ejemplo 169

1-Metilpiperidin-4-il N-(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato

El compuesto del título se preparó de 1,1-dióxido de 2-*terc*-butil-4-cloro-5-fenilisotiazol-3(2*H*)-ona y clorhidrato de 1-metilpiperidin-4-il β-alaninato en una manera similar como se describe para Ejemplo 164. Espectro de Masa: $[M+H]^+$ 450.12, $[M-H]^-$ 448.23.

Ejemplo 170

2-Mesitil-1-metiletil [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]acetato

El compuesto del título se preparó de ácido [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]acético y 1-mesitilpropan-2-ol. Espectro de Masa: $[M+H]^+$ 499.15, $[M-H]^-$ 497.98.

Ejemplo 171

4-Metoxibencil N-(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato

Ácido [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]acético (100mg, 0.30mmol), (4-metoxifenil)metanol (204mg, 1.48mmol), TEA (123μL) y DMAP (9mg, 0.074mmol) se disolvieron en DCM (10mL). Se agregaron DMF (81mL) y EDC (113mg, 0.59mmol), y la solución se agitó a 40°C de un día para otro. Se agregó K_2CO_3 acuoso (1M, 50mL), y la mezcla de reacción se extrajo con DCM. Las fases orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se purificó por HPLC preparativa proporcionando el compuesto del título (23mg, 17%). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.69 (s, 9H), 3.54 (s,

2H), 3.77 (s, 3H), 4.98 (s, 2H), 5.79 (t, 1H), 6.83 (d, 2H), 7.17 (d, 2H), 7.32-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7, 45.4, 55.5, 61.8, 67.6, 109.6, 114.2, 124.4, 127.0, 128.9, 130.1, 130.7, 131.5, 134.8, 159.2, 160.2, 168.7.

Ejemplo 172

4-Metoxifenil N-(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato

El compuesto del título se preparó de ácido [(2-*terc*-butil-1,1-dioxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]acético y 4-metoxifenol como se describe para Ejemplo 171, proporcionando el compuesto del título (28mg, 21%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 9H), 3.77 (s, 3H), 3.81 (d, 2H), 5.78 (t, 1H), 6.85 (dd, 4H), 7.44-7.51 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8, 45.6, 55.8, 61.9, 110.1, 114.7, 122.0, 124.5, 129.1, 130.2, 131.6, 134.8, 143.6, 157.8, 159.2, 167.8.

Actividad Biológica

Análisis de Reclutamiento de Co-Activador

El Dominio de Unión a Ligando (LBD) de LXRα (aminoácido 205-447) y LXRβ (aminoácido 216-461) humanos se produjo mediante técnicas recombinantes en *E coli*. Un fragmento del Co-Activador-1 de Receptor Esteroide humano (SRC-1) se produjo como un péptido sintético. Se utilizó un anticuerpo anti-6xHis acoplado con Europio (Eu^{3+}) para reconocer la marca His (***"the His-tag"***) en el LXR-LBD, y aloficocianina (APC) acoplada a estreptavidina se usó para reconocer el SRC-1 biotinilado. La unión de agonista a LXRα o LXRβ incrementa la afinidad de LXR hacia SRC-1 y, por consiguiente, lleva a Eu^{3+} y APC en estrecha proximidad. Eu^{3+} se excita a 337 nm y emite luz a 620 nm. Esta emisión, si se realiza en estrecha proximidad, excita APC a emitir luz a 665 nm.

Los compuestos (10mM) en DMSO se diluyeron (1/3) en DMSO en 10 concentraciones. Estas placas de dilución se diluyeron aún más en amortiguador {20mM [tris(hidroximetil)aminometano] pH 7.5, 0.125%

CHAPS {3-[(3-colamidopropil)dimetilamonio]-1-propanosulfonato}, 2mM DTT (ditiotreitol) y 0.05% BSA (albúmina sérica bovina)} con el fin de reducir la concentración de DMSO, 0.5 µl a 13.5 µl. A esto se agregaron 6 µl de mezcla de análisis, dando una concentración de análisis máxima de 83 µM, y las placas (placas con surco en V, de 384 pocillos) se incubaron a temperatura de la sala durante 60 a 80 minutos. La mezcla de análisis tenía las siguientes concentraciones finales: mezcla LXRα: 0.06 µg/mL anti-6x His Ab marcado con Eu, 1.15µg/mL estreptavidina APC, 30 nM péptido SRC-1 y 0.9 µg/mL LXRα en amortiguador, y mezcla LXRβ: 0.06 µg/mL anti-6x His Ab marcado con Eu, 1.15µg/mL estreptavidina APC, 90 nM péptido SRC-1 y 0.2 µg/mL LXRβ en amortiguador. Se realizaron lecturas de fluorescencia con resolución de tiempo (***"time-resolved fluorescence readings"***) en un lector Wallac Victor a 665 nm, seguidas por lectura a 615 nm. El ligando LXR, 22-R hidroxicolesterol o un compuesto interno a 50µM, se usó como el control 100%.

Análisis de Transactivación

Se prepararon vectores de expresión insertando el cADN (ADN complementario del dominio de unión a ligando de LXRα humano (aminoácido 205-447) y LXRβ (aminoácido 216-461) dentro del marco con 3' al dominio de unión de ADN del factor de transcripción GAL4 de levadura y la señal de localización nuclear del antígeno T de Polyoma Virus en el vector de expresión eucariota pSG5 (Stratagene). Los vectores de expresión resultantes pSGGAL-LXRα y pSGGAL-LXRβ se utilizaron en experimentos de co-transfección junto con el plásmido indicador de luciferasa pGL3 que contenía un promotor SV40 mínimo (Promega) y cinco copias del sitio de reconocimiento UAS GAL4. Se mezclaron 2.5 µg pSGGAL-LXRα o β con 25 µg pGL3 5xUAS y 22.5 µg pBluscript (Stratagene) en 0.95 mL de PBS helada que contenía aprox. 4-9 milj. de células de osteosarcoma. Luego de una incubación de cinco minutos sobre hielo la mezcla de ADN/células se sometió a electroporación en tubos de laboratorio de 0.4 cm a 960 µF, 230 V usando un electroporador BioRad y

se diluyó a 0.32 milj células/mL en DMEM completo [Dulbecco's Modified Eagle Medium sin rojo fenol, (Gibco 11880-028) que incluía 10% FBS (Suero Bovino Fetal), 1% PEST (Penicilina Estreptomicina), 20mM Hepes, 2mM L-Glutamina y 0.36% Glucosa Gibco 31966-021]. Células se por lo menos dos electroporaciones se combinaron (***"were pooled"***) con el fin evitar variaciones entre diferentes electroporaciones. 25 µl de células diluidas, electroporadas, se sembraron en placas de 384 pocillos (0.8×10^4 células / pocillo), se dejó que las células se adhirieran durante 2 horas a 37°C, 5% CO_2 en un incubador de cultivo celular. Los compuestos (10mM) en DMSO se diluyeron (1/3) en DMSO en 10 concentraciones. Estas placas de dilucción se diluyeron aún más DMEM completo sin rojo fenol (2.5μl a 97.5μl) con el fin de reducir la concentración de DMSO. 7 μl de esta se agregaron a las células electroporadas en placas de 384 pocillos, y se continuó la incubación durante 48 h en un incubador de cultivo celular, tras lo cual las células se desintegraron agregando 32 μl/pocillo de sustrato de luciferasa LucLite. Se midió la actividad de la luciferasa como luminiscencia en un lector Wallac Victor después de 15 minutos de incubación a temperatura de la sala. El ligando LXR, Tularik T0901317, o un estándar interno, a 1μM se utilizó como el control 100%.

Análisis *in vivo*

La separación de los efectos adipógenos indeseados y anti-aterógenos deseados de los ligandos LXR se probó en ratones C57 BL6 normales, a los cuales se administran los agentes de prueba durante tres días (4 dosis) en dosis orales fijas o diferentes. Se realizó alimentación por sonda gástrica una vez al día alrededor del mediodía, excepto la última dosis que se administró a las 0700 horas, 3 horas antes de la anestesia. 30 ratones se utilizaron en cada detección y éstos se dividieron en cinco grupos con seis animales en cada uno. Un grupo era el grupo de control, y los 4 grupos restantes se trataron con agentes de prueba en dosis fijas o diferentes. Los agentes de prueba se administraron por sonda gástrica una vez al día durante tres días en cuatro dosis totalmente.

Luego se tomaron muestras de sangre bajo anestesia para la determinación de los niveles plasmáticos de TG. Se extirpó el hígado para la determinación del peso del hígado y el contenido de TG. 20-50mg de tejido, hígado o intestino (primeros 2-3 cm distales del estómago) se congelarón rápidamente en nitrógeno líquido en el momento de la necropsia para análisis posterior de cualquier regulación por aumento de genes diana LXR, principalmente ABCA1, ABCG1, SREBP1c y FAS. Los tejidos se mantienen en un congelador a -80°C hasta el análisis.

Microcápsulas de acero inoxidable (Cat. No. 69989, QIAGEN) se agregaron a microtubos de recolección, una microcápsula por tubo, (Cat. No.19560, QIAGEN), mientras los tubos se mantenían sobre hielo seco. Los tejidos de pasaron a los microtubos de recolección, luego de lo cual se agregaron 750µl QIAzol (Cat. No.79306, QIAGEN), y entonces los tubos se pusieron en un Mixer Mill y se homogeneizaron durante 2 x 5 minutos a 25 Hz. Luego de la homogeneización la placa de 96 pocilos se centrifugó a 6000 x g durante un minuto a 4°C en una centrífuga Sigma 4K-15C. Se agregaron 150µl de cloroformo a todas las muestras, las cuales se agitaron vigorosamente durante 15 segundos y se incubaron a temperatura de la sala durante 2-3 y se centrifugaron de nuevo a 6000 x g durante 15 minutos. 200µl de la fase acuosa superior se transfirieron a tubos Square-well (Cat. No.19573, QIAGEN), y se agregó un volumen de 70% etanol y se mezcló pipeteando arriba y abajo. Luego de una incubación de 10 minutos sobre hielo, muestras de 250µl se cargaron en los pocillos de una placa con grupos de 96 pocillos (***"a 96-well culture cluster plate"***) (Cat. No. 3595, Corning Incorporated)

ARN se purificó usando un ABI Prism 6700 o ABI Prism 6100 de acuerdo con las recomendaciones de los fabricantes. Se eluyó ARN en 150µl con una concentración de 50-200ng/µl, y 10µl de éste se analizó mediante electroforesis en gel de agarosa (gel TBE al 1% no desnaturalizante) para verificar la calidad del ARN. Se realizó síntesis de cADN usando el High-Capacity Archive Kit (Cat. No 4322171, Applied Biosystems) de acuerdo con las recomendaciones de los fabricantes,

mediante cebadores aleatorios, en un volumen de reacción total de 50µl/muestra. Se determinaron los niveles de mARN de expresión génica mediante PCR en tiempo real (7500 Real-time PCR system, Applied Biosystems). Mezcla Taqman universal PCR master (Cat. No. 4305719, Applied Biosystems) se utilizó en una reacción de 25µl que contenía 400nM de cada cebador diana, 100nM de cada uno de los cebadores de control (36B4), 200nM de la sonda diana, 100nM de la sonda de control (36B4) y 2.5-10ng de cADN de muestra. Se determinaron los ciclos umbral (Ct) para el gen de control endógeno 36B4 y los genes diana, y se calcularon los niveles de mARN relativos usando el método Ct comparativo y se expresaron como inducción múltiplo.

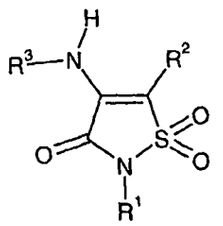
Se usaron los siguientes cebadores y sondas: ABCA1 avance; 5'-AAGGGTTTCTTTGCTCAGATTGTC-3', ABCA1 inverso; 5'-TGCCA AAGGGTGGCACA-3', ABCA1 sonda; 5'-FAM-CCAGCTGTCTTTGTTTGCATTGCCC-TAMRA-3', ABCG1 avance; 5'-CCATGAATGCCAGCAGCTACT-3', ABCG1 inverso; 5'-CACTGACACGCACACGGACT-3', ABCG1 sonda; 5'-FAM-TGCCGCAATGACGGAGCCC-TAMRA-3', FAS avance; 5'-GGCATCATTGGGCACTCCTT-3', FAS inverso; 5'-GCTGCAAGCACAGCCTCTCT-3', FAS sonda; 5'-FAM-CCATCTGCATAGCCACAGGCAACCTC-TAMRA-3', SREBP1c avance; 5'-GGAGCCATGGATTGCACATT-3', SREBP1c inverso; 5'-CCTGTCTCACCCCCAGCATA-3', SREBP1c sonda; 5'-FAM-CAGCTCATCAACAACCAAGACAGTGACTTCC-TAMRA-3', 36B4 avance; 5'-GAGGAATCAGATGAGGATATGGGA-3', 36B4 inverso; 5'-AAGCAGGCTGACTTGGTTGC-3', 36B4 sonda; 5'-VIC-TCGGTCTCTCGACTAATCCCGCCAA-TAMRA-3'. A partir de relaciones de respuesta a la dosis, se determinaron valores de selectividad (potencias relativas) para discriminar entre la regulación por aumento intestinal primaria de genes diana LXR y las elevaciones TG hepáticas y plasmáticas indeseadas, respectivamente.

Los compuestos de fórmula I tienen una EC_{50} de menos de 50 µmol/l para LXRα y/o β en análisis de reclutamiento de co-activador y/o análisis de gen indicador. Por ejemplo, los compuestos de Ejemplo 6 y Ejemplo 10 tienen EC_{50} para LXRα de 0.58 µmol/l y 1.42 µmol/l en el análisis de reclutamiento de co-activador, respectivamente, y los compuestos de Ejemplos 2 y Ejemplo 7 tienen EC_{50} para LXRα de 1.36 µmol/l y 0.27 µmol/l en el análisis de gen indicador. Adicionalmente, los compuestos de la presente invención exhiben efectos farmacológicos favorables *in vivo*.
Los compuestos de la presente invención poseen asimismo un prometedor perfil toxicológico.

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REIVINDICACIONES

1. Un compuesto de fórmula general (I)



fórmula (I)

o su sal farmacéuticamente aceptable,

en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

o R^1 es cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es fenilo o heteroarilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes independientemente seleccionados de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes independientemente seleccionados de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^1 es fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más

de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^cC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^2 representa

Fenilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$;

o R^3 es

MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$,

$NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$ $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

y en las anteriores definiciones

X representa un grupo alquilo saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono en donde dicho grupo alquilo puede interrumpirse opcionalmente por O, S, SiR^bR^b, S(O), SO_2, C(O), NR^a, OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2;

Y el cual se une al nitrógeno en la posición 2 del 1,1-dióxido de isotiazol-3(2*H*)-ona y representa un grupo alquileno saturado o insaturado, recto o ramificado, con 1 a 3 átomos de carbono en donde dicho grupo alquilo puede interrumpirse o terminarse opcionalmente por uno de los siguientes: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^cC(O)$, $C(O)NR^c$, NR^c y/o Y se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: OH, F, CN, NR^aR^a, C_1-C_4alquilo, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$ o SO_2R^b;

Z se une a E o Het^4 y uno de los siguientes: Q, Het^1, R o Het^2, y representa un grupo alquileno saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono en donde dicho grupo alquileno puede interrumpirse o terminarse opcionalmente por uno de los siguientes: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2, o es uno de los siguientes: O, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, NR^a, SO_2NR^a, NR^aSO_2 y/o Z se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: OH, F, CN, NR^cR^c, $C(O)R^c$, OR^b, SR^c, $SiR^bR^bR^b$, $S(O)R^c$, SO_2R^c, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, OR^b;

M representa un anillo monocarbocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un sistema de anillo bicíclico no aromático o parcialmente aromático, saturado o insaturado, compuesto de 8, 9 ó 10 átomos de carbono;

E representa un anillo monocarbocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono o un sistema de anillo bicíclico no aromático o parcialmente aromático, saturado o insaturado, compuesto de 8, 9 ó 10 átomos de carbono, y el anillo se une, a menos que se especifique lo contrario, a través de su parte no aromática a nitrógeno en la posición 4 en el 1,1-dióxido de la isotiazol-3(2*H*)-on;

A representa un anillo monocíclico aromático, compuesto de 6 átomos de carbono o un sistema de anillo bicíclico aromático, compuesto de 10 átomos de carbono;

P se une a nitrógeno en la posición 4 en el 1,1-dióxido de la isotiazol-3(2*H*)-ona y representa un grupo alquileno saturado o insaturado, recto o ramificado, con 1 a 6 átomos de carbono, en donde el grupo alquileno se interrumpe o se termina opcionalmente por uno de los siguientes: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a, NR^aSO_2 y/o P se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, $C(O)R^c$, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, fenilo, fenilC_1-C_3alquilo, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, NR^aR^a, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o OR^b;

Q representa un anillo monocíclico no aromático, saturado o insaturado, compuesto de 3, 4, 5, 6, 7 u 8 átomos de carbono, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

R representa un grupo fenilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN,

NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

T se une a M, Het^3, A o Het^5 y uno de los siguientes: Q, Het^1, R o Het^2; y representa metileno o es uno de los siguientes: O, NR^a, S, SiR^bR^b, S(O), SO_2, C(O), OC(O), C(O)O, $NR^aC(O)$, $C(O)NR^a$, SO_2NR^a o NR^aSO_2;

Het^1 representa un anillo monocíclico de 3, 4, 5, 6, 7, 8, 9 ó 10 miembros, no aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono seleccionado independientemente de uno o más de por ejemplo nitrógeno, oxígeno o azufre, y en donde el anillo se sustituye opcionalmente por uno o más de los siguientes, seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

Het^2 representa un anillo monocíclico de 5 ó 6 miembros, aromático, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono seleccionado independientemente de uno o más de por ejemplo nitrógeno, oxígeno y azufre, y que se sustituye por uno o más de los siguientes, seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, fenilC_1alquilo, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, OSO_2R^b, $NR^aC(O)NR^aR^a$, $SO_2NHC(O)R^b$, o C_1-C_4alquilo, sustituido opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $NR^aSO_2R^b$, $SO_2NR^aR^a$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

Het^3 representa un anillo monocíclico de 3, 4, 5, 6, 7, 8, 9 ó 10 miembros, no aromático, saturado o insaturado o un sistema de anillo bicíclico de 9 ó 10 miembros, no aromático o parcialmente aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo monocíclico o sistema de anillo bicíclico es un elemento distinto de carbono seleccionado independientemente de uno o más de por ejemplo nitrógeno, oxígeno o azufre;

Het^4 representa un anillo monocíclico de 3, 4, 5, 6, 7, 8, 9 ó 10 miembros, no aromático, saturado o insaturado o un sistema de anillo bicíclico, de 9 ó 10 miembros, no aromático o parcialmente aromático, saturado o insaturado, en el cual uno o más de los átomos en el anillo monocíclico o sistema de anillo bicíclico es un elemento distinto de carbono seleccionado independientemente de uno o más de, por ejemplo, nitrógeno, oxígeno o azufre, y el anillo se une, a menos que se especifique lo contrario, a través de su parte no aromática a nitrógeno en la posición 4 del 1,1-dióxido de isotiazol-3(2*H*)-ona;

Het^5 representa un anillo monocíclico de 5 ó 6 miembros, aromático o un sistema de anillo bicíclico, de 9 ó 10 miembros, aromático, en el cual uno o más de los átomos en el anillo monocíclico o sistema de anillo bicíclico es un elemento distinto de carbono, seleccionado independientemente de uno o más de por ejemplo nitrógeno, oxígeno o azufre;

R^a representa independientemente H o una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F;

R^b representa independientemente una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F; y

R^c representa independientemente H o una cadena C_1-C_4alquilo saturado o insaturado, recto o ramificado, sustituido opcionalmente por uno o más F.

2. Un compuesto de acuerdo con la reivindicación 1 o su sal farmacéuticamente aceptable, en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o $C(O)R^b$;

o R^1 es cicloalquilo o heterociclilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o $C(O)R^b$;

o R^1 es fenilo o heteroarilo, que se sustituyen cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo sustituido opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

o R^1 es cicloalquilY o heterociclilY en donde cicloalquilo o heterociclilo se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

o R^1 es fenilY o heteroarilY, en donde fenilo o heteroarilo se sustituyen cada uno opcionalmente por uno o más de los

siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$;

R^2 representa

fenilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, I, Br), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$.

3. Un compuesto de acuerdo con la reivindicación 2 o su sal farmacéuticamente aceptable, en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $C(O)NR^aR^a$, $NR^aC(O)R^b$, $C(O)OR^a$, $OC(O)R^b$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

4. Un compuesto de acuerdo con la reivindicación 3 o su sal farmacéuticamente aceptable, en donde

R^1 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b o $C(O)R^b$.

5. Un compuesto de acuerdo con la reivindicación 1 o su sal farmacéuticamente aceptable, en donde

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

6. Un compuesto de acuerdo con la reivindicación 1 o su sal farmacéuticamente aceptable, en donde

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes

seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

7. Un compuesto de acuerdo con la reivindicación 1 o su sal farmacéuticamente aceptable, en donde

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 cada uno se sustituye opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

8. Un compuesto de acuerdo con la reivindicación 2 o su sal farmacéuticamente aceptable, en donde

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

9. Un compuesto de acuerdo con la reivindicación 2 o su sal farmacéuticamente aceptable, en donde

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituye cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1,

Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

10. Un compuesto de acuerdo con la reivindicación 2 o su sal farmacéuticamente aceptable, en donde

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a,

OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

11. Un compuesto de acuerdo con la reivindicación 3 o su sal farmacéuticamente aceptable en donde

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

12. Un compuesto de acuerdo con la reivindicación 3 o su sal farmacéuticamente aceptable, en donde

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$,

$NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

13. Un compuesto de acuerdo con la reivindicación 3 o su sal farmacéuticamente aceptable, en donde

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados

independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

14. Un compuesto de acuerdo con la reivindicación 4 o su sal farmacéuticamente aceptable en donde

R^3 representa

X que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$, $NR^aC(O)NR^aR^a$, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$ o $NR^aC(O)NR^aR^a$.

15. Un compuesto de acuerdo con la reivindicación 4 o su sal farmacéuticamente aceptable, en donde

R^3 representa

MP o Het^3P en donde M y Het^3 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$,

$C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y en donde M o Het^3 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (Cl, F, Br, I), OH, CN, NR^aR^a OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$;

o R^3 es AP o Het^5P en donde A y Het^5 se sustituye cada uno opcionalmente por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NO_2, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, $NR^aC(O)NR^aR^a$, Q, QT, Het^1, Het^1T, R, RT, Het^2, Het^2T, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

16. Un compuesto de acuerdo con la reivindicación 4 o su sal farmacéuticamente aceptable, en donde

R^3 representa

E o Het^4 se sustituyen cada uno opcionalmente en el anillo no aromático por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $OC(O)NR^aR^a$, $NR^aC(O)OR^b$, $NR^aC(O)NR^aR^a$, Q, QZ, Het^1, Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$,

y E o Het^4 se sustituye cada uno opcionalmente en el anillo aromático por uno o más de los siguientes seleccionados independientemente de: halógeno (F, Cl, Br, I), OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, OSO_2R^b, $SO_2NR^aC(O)R^b$, Q, QZ, Het^1 , Het^1Z, R, RZ, Het^2, Het^2Z, o C_1-C_4alquilo, que se sustituye opcionalmente por uno o más de los siguientes seleccionados independientemente de: F, OH, CN, NR^aR^a, OR^b, SR^b, $SiR^bR^bR^b$, $S(O)R^b$, SO_2R^b, $C(O)R^b$, $NR^aC(O)R^b$, $C(O)NR^aR^a$, $OC(O)R^b$, $C(O)OR^a$, $SO_2NR^aR^a$, $NR^aSO_2R^b$, $NR^aC(O)OR^b$, $OC(O)NR^aR^a$ o $NR^aC(O)NR^aR^a$.

17. Un compuesto de acuerdo con la reivindicación 1, en la cual R^1 se selecciona de etilo, isopropilo, n-butilo, *terc*-butilo, ciclopentilo, hexilo, bencilo, 2-metoxietilo, piridin-2ilmetilo, piridin-3-ilmetilo, piridin-4-ilmetilo, tetrahidrofuran-2-ilmetilo, 2-(3-fluorofenil)etilo, isobutilo, 4-fluorobencilo, (5-metilisoxazol-3-il)metilo o (metiltio)metilo;

R^2 es fenilo; y

R^3 se selecciona de n-butilo, n-hexilo, bencilo, 3-[3-(hidroximetil)fenoxi]propilo, 4-fenilbutilo, 3-(2-metoxifenoxi)propilo, 3-[4-(hidroximetil)fenoxi]propilo, 3-(2-fluorofenoxi)propilo, 3-(2-clorofenoxi) propilo, 3-(3-metoxifenoxi)propilo, 3-(piridin-3-iloxi)propilo, 3-(piridin-4-iloxi)propilo, 1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 3-(feniltio)propilo, 3-fenoxipropilo, 3-(3-clorofenoxi)propilo, 3-(3-fluorofenoxi)propilo, 3-(4-fluorofenoxi)propilo, 1-[4-(trifluorometil) pirimidin-2-il]piperidin-4-ilo, *cis*-4-hidroxiciclohexilo, 4-fenoxibutilo, 3-[(1-oxidopiridin-3-il)oxi]propilo, 3-(4-metoxifenoxi)propilo, 4,4-difluorociclohexilo, 2-fenoxietilo, 2-feniletilo, 4-(difluorometoxi)bencilo, *trans*-4-hidroxiciclohexilo, 3-hidroxipropilo, 2,3-dihidro-1,4-benzodioxin-2-ilmetilo, 4-hidroxiciclohexilo, 3-(4-clorofenoxi)propilo, 1,3-benzodioxol-5-ilmetilo, 2,3-dihidro-1*H*-inden-2-ilo, 2-(morfolin-4-il)etilo, 3-(4-isopropilfenoxi)propilo, 3-[bencil(butil)amino]propilo, 3-(3,5-dipropoxifenoxi)propilo, 2,2-difeniletilo, 2-(1*H*-imidazol-4-il)etilo, 4-morfolin-4-ilbencilo, 3-(2-metoxietoxi)propilo, 3-morfolin-4-ilpropilo, 2-metoxietilo, tetrahidro-2H-piran-4-ilo, 4-hidroxiciclohexilo, 4-metoxibencilo, 3-(3-hidroxifenoxi)propilo, 3-(3-acetamidofenoxi)propilo, 3-(4-*N*,*N*-dimetilaminocarbonilmetilfenoxi)propilo, 3-(3-carboximetilfenoxi)propilo, 3-(3-metoxicarbonilmetilfenoxi)propilo, 3-(3-metoxicarbonilfenoxi)propilo, 3-(4-carboximetilfenoxi)propilo, 3-(4-metoxicarbonilmetilfenoxi)propilo, 3-(3-acetilaminofenoxi)propilo, 3-(4-hidroxifenilcarboxi)propilo, 3-(4-carboxifenoxi)propilo, 1-(2-nitriloetil) piperidin-4-ilo, isopropilo, etilo, 2,2-dimetilpropilo, *terc*-butilo, 2-(2-metoxietoxi)etilo, 2-hidroxietilo, 2,2,2-trifluoroetilo, metil etanoilglicinato, 2,3-dihidro-1,4-benzodioxin-6-ilmetilo, 1,3,5-trimetil-1*H*-pirazol-4-ilmetilo, 3-(3,5-dimetil-1*H*-pirazol-1-il)propilo, 2-(pirrolidin-3-iltio)etilo, 2-[1-(*terc*-butoxicarbonil)pirrolidin-3-il]etilo, 2-[1-(*terc*-butoxicarbonil) pirrolidin-3-il]etilo, 2-{[1-(*terc*-butoxicarbonil) pirrolidin-3-il]tio}etilo, 2-piridin-2-iletilo, 2-{[3-cloro-5-(trifluorometil) piridin-2-il]amino}etilo, 2-{[5-(trifluorometil)piridin-2-il]oxi}etilo, 3-(piridin-2-iloxi)propilo, 1-(*terc*-butoxicarbonil)piperidin-4-ilo, 1-acetilpiperidin-4-ilo, piperidin-4-ilo, 1-

metilpiperidin-4-ilo, 1-isobutirilpiperidin-4-ilo, 1-piridin-2-ilpiperidin-4-ilo, 1-(5-fluoropiridin-2-il)piperidin-4-ilo, 1-(5-cloropiridin-2-il)piperidin-4-ilo, 1-(5-metilpiridin-2-il)piperidin-4-ilo, 1-[4-(trifluorometil)piridin-2-il] piperidin-4-ilo, 1-[5-(trifluorometil)piridin-2-il]piperidin-4-ilo, 1-(6-cloropiridin-3-il)piperidin-4-ilo, 1-piridazin-3-ilpiperidin-clorofenil)etilo, 3-(3-carboxifenoxi)propilo, 3-[3-(2-metoxi-2-oxoetil)fenoxi]propilo, 3-[4-(2-metoxi-2-oxoetil)fenoxi]propilo, 3-{4-[2-(dimetilamino)-2-oxoetil]fenoxi}propilo, 3-[(4-hidroxibenzoil)oxi]propilo, 2-{2-[(metilsulfonil)oxi]fenoxi}etilo, 2-{4-[(metilsulfonil)oxi]fenoxi}etilo, 2-[2-(metoxicarbonil)fenoxi]etilo, 2-(4-clorofenoxi)etilo, 2-[3-(trifluorometoxi)fenoxi]etilo, 2-{[3-(trifluorometoxi)fenil]tio}etilo, 2-(bencilamino)-2-oxoetilo o 2-{[3-(difluorometoxi)bencil]amino}-2-oxoetil-4-ilo, 1-(6-cloropiridazin-3-il)piperidin-4-ilo, 1-(6-metoxipiridazin-3-il) piperidin-4-ilo, 1-(4-cianobencil)piperidin-4-ilo, 1-[2-(trifluorometil) benzoil]piperidin-4-ilo, 1-[3-(metoxicarbonil)bencil]piperidin-4-ilo, 1-bencilpiperidin-4-ilo, 1-benzoilpiperidin-4-ilo, 1-(fenilacetil)piperidin-4-ilo, 1-(4-cianobenzoil)piperidin-4-ilo, 1-(3,4-difluorobenzoil)piperidin-4-ilo, 1-(2-feniletil)piperidin-4-ilo, 1-(2-feniletil)piperidin-4-ilo, 1-bencilpirrolidin-3-ilo, 4-{[4-(trifluorometil)fenil]tio}ciclohexilo, 1-[(5-metilisoxazol-3-il)metil]piperidin-4-ilo, 1-(2-cloro-6-metilisonicotinoil)piperidin-4-ilo, 1-[(2-cloropiridin-3-il)carbonil]piperidin-4-ilo, 2-{4-[(metilsulfonil)oxi]fenil} etilo, 2-[4-(aminosulfonil)fenil]etilo, 2-(4- cianofenil)etilo, 2-(3-cianofenil)etilo, 2-[2-(trifluorometoxi)fenil]etilo, 2-[3-(trifluorometoxi) fenil]etilo, o 3-[(1-metilpiperidin-4-il)oxi]-3-oxopropilo, 2-(3,4-dimetoxifenil)etilo, 2-(3-cloro-4-metoxifenil)etilo, 2-(4-hidroxi-3,5-dimetoxifenil)etilo, 2-(4-metoxifenoxi)-2-oxoetilo, 2-[(4-metoxibencil)oxi]-2-oxoetilo, 2-(2-mesitiletoxi)-2-oxoetilo, 2-(2-mesitil-1-metiletoxi)-2-oxoetilo, 3-oxo-3-fenoxipropilo, 3-oxo-3-[4-(trifluorometoxi)fenoxi] propilo, 2-{[(2,6-dimetilfenil)acetil]oxi}etilo, 4-(2,6-dimetilfenoxi)-4-oxobutilo, (5-metilisoxazol-3-il)metilo, 2-(2-aminopiridin-4-il)etilo, 2-piridin-4-iletilo, 2-piridin-3-iletilo, 2-(3,5-dimetilisoxazol-4-il)etilo o 2-(3,5-dimetil-1*H*-pirazol-4-il)etilo, o 1-piridin-2-ilazetidin-3-ilo.

18. Un compuesto seleccionado de uno o más de los siguientes:

1,1-dióxido de 2-*terc*-butil-4-({3-[3-(hidroximetil)fenoxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({3-[4-(hidroximetil)fenoxi]propil} amino)-5-fenilisotiazol-3(2*H*)-ona

N-(3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetamida

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

2-(4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)-N,N-dimetilacetamida

1,1-dióxido de 2-*terc*-butil-4-{[3-(2-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

ácido (3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acético

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-3-iloxi)propil]amino} isotiazol-3(2*H*)-on

metil (3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-4-iloxi)propil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]piperidin-4-il}amino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-ciclopentil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(feniltio)propil]amino}isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(3-fenoxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

metil 3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoato

1,1-dióxido de 2-bencil-5-fenil-4-[(4-fenilbutil)amino]isotiazol-3(2*H*)-ona

ácido (4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acético

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-fluorofenoxi)propil]amino}-5-fenilisotiazol-3 (2*H*)-ona

metil (4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}fenil)acetato

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-fluorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-({1-[4-(trifluorometil)pirimidin-2-il] piperidin-4-il} amino)isotiazol-3(2*H*)-ona

N-(3-{3-[(2-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]propoxi}fenil)acetamida

3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] propil 4-hidroxibenzoato

1,1-dióxido de 4-(bencilamino)-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-[2-(3-fluorofenil)etil]-5-fenil-4-[(4-fenilbutil)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(cis-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(4-fenoxibutil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({3-[(1-oxidopiridin-3-il)oxi]propil}amino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-ciclopentil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-metoxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(4,4-difluorociclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-4-[(2-fenoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(tetrahidrofuran-2-ilmetil) isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(bencilamino)-2-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-(hexilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-5-fenil-4-[(2-feniletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-{[4-(difluorometoxi)bencil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(trans-4-hidroxiciclohexil)amino]-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(3-hidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-3-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,3-dihidro-1,4-benzodioxin-2-ilmetil) amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-hidroxiciclohexil)amino]-5-fenilisotiazol-3(2*H*)-ona

ácido 4-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoico

3-{4-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}propanonitrilo

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-clorofenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-4-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-(2,3-dihidro-1*H*-inden-2-ilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(2-morfolin-4-iletil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(4-isopropilfenoxi)propil]amino}-5-fenilisotiazol-3-(2*H*)-ona

1,1-dióxido de 4-({3-[bencil(butil)amino]propil}amino)-2-*terc*-butil-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3,5-dipropoxifenoxi)propil]amino}-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,2-difeniletil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-etil-4-{[2-(1H-imidazol-4-il)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-morfolin-4-ilbencil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-{[3-(2-metoxietoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(3-morfolin-4-ilpropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(2-metoxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-(2-metoxietil)-5-fenil-4-(tetrahidro-2*H*-piran-4-ilamino)isotiazol-3(2*H*)-ona

1,1-dióxido de 4-(hexilamino)-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(4-hidroxiciclohexil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1,3-benzodioxol-5-ilmetil)amino]-2-(2-metoxietil)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-butil-4-[(4-metoxibencil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 5-fenil-4-[(4-fenilbutil)amino]-2-(piridin-2-ilmetil)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3-hidroxifenoxi)propil]amino}-5-fenilisotiazol-3(2*H*)-ona

ácido 3-{3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]propoxi}benzoico

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil}fenil metanosulfonato

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}bencenosulfonamida

1,1-dióxido de 2-*terc*-butil-4-({1-[3-cloro-5-(trifluorometil)piridin-2-il] piperidin-4-il} amino)-5-fenilisotiazol-3(2*H*)-ona

terc-butil 3-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4- il)amino]etil}azetidin-1-carboxilato

2-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenil metanosulfonato

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

4-({4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]piperidin-1-il}metil)benzonitrilo

1,1-dióxido de 2-*terc*-butil-4-(isopropilamino)-5-fenilisotiazol-3(2*H*)-ona

4-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenil metanosulfonato

terc-butil 3-({2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etil}tio)pirrolidin-1-carboxilato

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[3-(piridin-2-iloxi)propil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2-{[3-cloro-5-(trifluorometil)piridin-2-il] amino}etil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({1-[2-(trifluorometil)benzoil] piperidin-4-il}amino)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(5-metilpiridin-2-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(6-cloropiridazin-3-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

terc-butil 4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-carboxilato

metil 2-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etoxi}benzoato

metil 3-({4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-il}metil)benzoato

1,1-dióxido de 2-*terc*-butil-4-{[1-(6-metoxipiridazin-3-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({1-[(2-cloropiridin-3-il)carbonil]piperidin-4-il}amino)-5-fenilisotiazol-3(2*H*)-ona

2-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etoxi}fenil metanosulfonato

1,1-dióxido de 2-*terc*-butil-4-{[1-(6-cloropiridin-3-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-[(1-bencilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

4-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino] etil}bencenosulfonamida

4-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

1,1-dióxido de 2-*terc*-butil-4-(etilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-({1-[(5-metilisoxazol-3-il)metil]piperidin-4-il}amino)-5-fenilisotiazol-3(2*H*)-ona

N^2-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-N^1-[3-(difluorometoxi)bencil]glicinamida

1,1-dióxido de 4-[(1-benzoilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[1-(fenilacetil)piperidin-4-il]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(1-piridin-2-ilpiperidin-4-il)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(1-piridazin-3-ilpiperidin-4-il)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[2-(piridin-3-iloxi)etil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(5-fluoropiridin-2-il)piperidin-4-il] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[3-(3,5-dimetil-1H-pirazol-1-il)propil] amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(2-cloro-6-metilisonicotinoil)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[1-(5-cloropiridin-2-il)piperidin-4-il]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({1-[4-(trifluorometil)piridin-2-il] piperidin-4-il}amino)isotiazol-3(2*H*)-ona

4-({4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]piperidin-1-il}carbonil)benzonitrilo

1,1-dióxido de 2-*terc*-butil-4-{[1-(3,4-difluorobenzoil)piperidin-4-il] amino}-5-fenilisotiazol-3 (2*H*)-ona

1,1-dióxido de 4-[(1-acetilpiperidin-4-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

3-{2-[(2-isopropil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}benzonitrilo

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[2-(trifluorometoxi)fenil]etil} amino)isotiazol-3(2*H*)-ona

4-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etoxi}fenil metanosulfonato

1,1-dióxido de 4-[(1-bencilpirrolidin-3-il)amino]-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-({1-[3-cloro-5-(trifluorometil)piridin-2-il]azetidin-3-il} amino)-2-isopropil-5-fenilisotiazol-3 (2*H*)-ona

N^1-bencil-N^2-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinamida

1,1-dióxido de 2-*terc*-butil-4-[(1-isobutirilpiperidin-4-il)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-piridin-2-iletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[2-(2-clorofenil)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[1-(2-feniletil)piperidin-4-il]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[3-(trifluorometil)fenil]etil}amino) isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(4-{[4-(trifluorometil)fenil]tio} ciclohexil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-{[3-(trifluorometoxi)fenil]tio}etil) amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[2-(4-clorofenoxi)etil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({1-[5-(trifluorometil)piridin-2-il] piperidin-4-il} amino)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[3-(trifluorometoxi)fenoxi]etil} amino)isotiazol-3(2*H*)-ona

terc-butil 3-{2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]etoxi}azetidin-1-carboxilato

1,1-dióxido de 2-*terc*-butil-4-[(2,2-dimetilpropil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-(*terc*-butilamino)-5-fenilisotiazol-3(2*H*)-ona

metil ({[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4- il) amino]acetil}amino)acetato

1,1-dióxido de 2-*terc*-butil-5-fenil-4-(piperidin-4-ilamino)isotiazol-3 (2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(1-metilpiperidin-4-il)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2-hidroxietil)amino]-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(bifenil-2-iltio)etil]amino}-2-*terc*-butil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[2-(pirrolidin-3-iltio)etil]amino} isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[(5-metil-3-fenilisoxazol-4-il)metil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-{[(1,3,5-trimetil-1H-pirazol-4-il)metil] amino}isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2-{[5-(trifluorometil)piridin-2-il]oxi} etil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-({2-[4-(trifluorometoxi)fenil]etil} amino)isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-5-fenil-4-[(2,2,2-trifluoroetil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-[(2,3-dihidroxipropil)amino]-5-fenilisotiazol-3(2*H*)-ona

3-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] propanonitrilo

1,1-dióxido de 4-{[2-(3,4-dimetoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(3-cloro-4-metoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

4-{2-[(2-isobutil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il) amino]etil}fenil metanosulfonato

1,1-dióxido de 2-isopropil-5-fenil-4-[(1-piridin-2-ilpiperidin-4-il)amino] isotiazol-3(2*H*)-ona

4-(2-{[2-(4-fluorobencil)-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il]amino}etil)fenil metanosulfonato

1,1-dióxido de 2-isopropil-4-(isopropilamino)-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(1-piridin-2-ilazetidin-3-il)amino] isotiazol-3(2*H*)-ona

1,1-dióxido de 2-*terc*-butil-4-{[(5-metilisoxazol-3-il)metil]amino}-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(4-hidroxi-3,5-dimetoxifenil)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(2-aminopiridin-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(2-piridin-4-iletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 2-isopropil-5-fenil-4-[(2-piridin-3-iletil)amino]isotiazol-3(2*H*)-ona

1,1-dióxido de 4-{[2-(3,5-dimetilisoxazol-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3 (2*H*)-ona

4-[2-({2-[(5-metilisoxazol-3-il)metil]-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il}amino)etil]fenil metanosulfonato

1,1-dióxido de 4-{[2-(3,5-dimetil-1H-pirazol-4-il)etil]amino}-2-isopropil-5-fenilisotiazol-3(2H)-ona

4-[2-({2-[(metiltio)metil]-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il}amino)etil]fenil metanosulfonato

2,6-dimetilfenil 4-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]butanoato

2-mesitiletil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato

2-[(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino] etil (2,6- dimetilfenil)acetato

fenil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato

4-(trifluorometoxi)fenil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato

1-metilpiperidin-4-il N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)-beta-alaninato

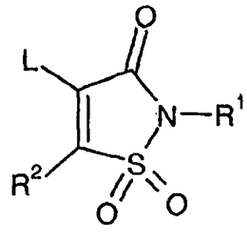
2-mesitil-1-metiletil [(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)amino]acetato

4-metoxibencil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato

4-metoxifenil N-(2-*terc*-butil-1,1-dióxido-3-oxo-5-fenil-2,3-dihidroisotiazol-4-il)glicinato

o su sal farmacéuticamente aceptable.

19. Un proceso para la preparación de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-18, en donde R^1, R^2 y R^3 son como se definen en la reivindicación 1, que comprende el paso de hacer reaccionar (a) un compuesto de fórmula (VI),



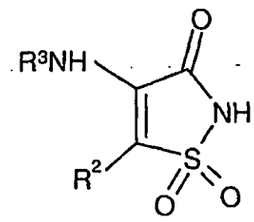
(VI)

en donde R^1 y R^2 son como se definen en la reivindicación 1 y L es un grupo saliente tal como Cl, Br, I, p-toluenosulfonato, metanosulfonato o trifluorometanosulfonato, con un compuesto de fórmula (VII,

$$R^3NH_2 \text{ (VII)}$$

en donde R^3 es se define en la reivindicación 1, opcionalmente en la presencia de un disolvente orgánico inerte tal como dimetilformamida, o

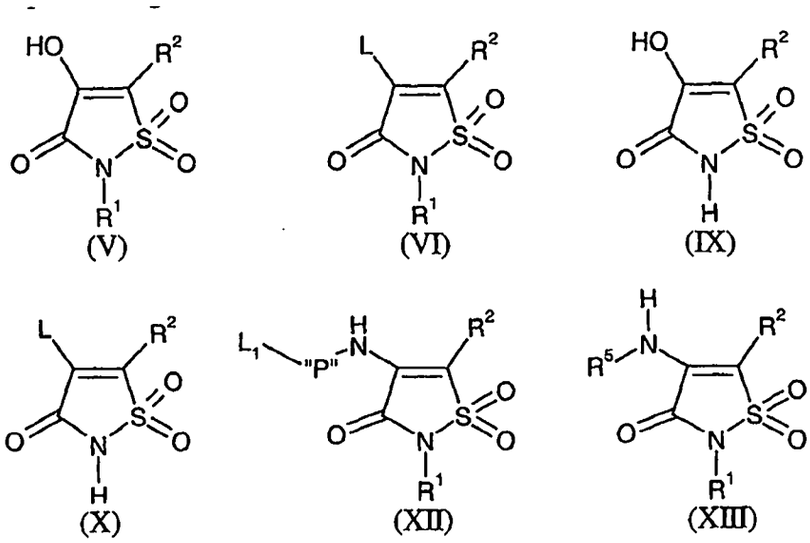
(b) un compuesto de fórmula (X),



(X)

en donde R^2 y R^3 son como se definen en la reivindicación 1, o bien con un agente alquilante tal como R^1L, en donde R^1 es como se define en la reivindicación 1 y L es un grupo saliente tal como Cl, Br, I, p-toluenosulfonato, metanosulfonato o trifluorometanosulfonato, o con R^1OH, en donde R^1 es como se define en la reivindicación 1, usando condiciones de Mitsunobu.

20. Un compuesto de fórmula general (V), (VI), (IX), (X), (XII) o (XIII)



(V) (VI) (IX)

(X) (XII) (XIII)

o su sal farmacéuticamente aceptable,

en donde R^1 es como se define en la reivindicación 1, R^2 es como se define en la reivindicación 1, L es un grupo saliente apropiado tal como Cl, Br, I, p-toluenosulfonato, metanosulfonato o trifluorometanosulfonato, "P" es como se define para P en la reivindicación 1, Li es OH, NH_2, SH o un grupo saliente apropiado tal como Cl, Br, I, p-toluenosulfonato, metanosulfonato o trifluorometanosulfonato, y R^5 es Het^4 o E en donde Het^4 y E son como se definen en la reivindicación 1, con la salvedad de que se excluyen los siguientes compuestos: 1,1-dióxido de 4-hidroxi-5-fenilisotiazol-3(2*H*)-ona, 1,1-dióxido de 5-(4-aminofenil)-4-hidroxi-2-metilisotiazol-3(2*H*)-ona, 1,1-dióxido de 4-hidroxi-2-metil-5-(4-nitrofenil)isotiazol-3(2*H*)-ona, 1,1-dióxido de 4-hidroxi-2-metil-5-fenilisotiazol-3(2*H*)-ona, 1,1-dióxido de 5-(3,4-diclorofenil)-4-hidroxiisotiazol-3(2*H*)-ona, 1,1-dióxido de 2-bencil-4-hidroxi-5-fenilisotiazol-3(2*H*)-ona, y 1,1-dióxido de 4-hidroxi-2-(4-metilfenil)-5-fenilisotiazol-3(2*H*)-ona.

21. Una formulación farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-18, o su sal apropiada farmacéuticamente aceptable, en mezcla con un coadyuvante, diluyente y/o excipiente farmacéuticamente aceptable.

22. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-18, o su sal apropiada farmacéuticamente aceptable, como un medicamento en terapia.

23. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-18, o su sal apropiada farmacéuticamente aceptable, como un medicamento en tratar enfermedades asociadas con una necesidad de modulación de los receptores hormonales nucleares LXR α y/o β; enfermedad cardiovascular, aterosclerosis, hipercolesterolemia, enfermedades asociadas con una necesidad de intensificar el transporte reverso de colesterol, enfermedades asociadas con una necesidad de disminuir la absorción del colesterol en el intestino, enfermedades asociadas con una necesidad de incrementar los niveles de colesterol HDL, enfermedades asociadas con una necesidad de

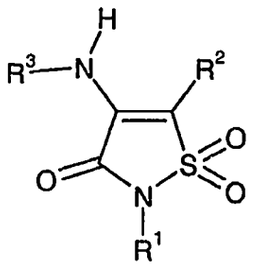
de reducir los niveles de colesterol LDL; enfermedades inflamatorias, enfermedad de Alzheimer, arteriosclerosis, diabetes tipo 2, afecciones asociadas con una necesidad de mejorar la función HDL; o trastornos lipídicos (dislipidemia) asociados o no con resistencia a la insulina.

24. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-18, o su sal apropiada farmacéuticamente aceptable, para la fabricación de un medicamento para la modulación de los receptores hormonales nucleares LXR α y/o β; enfermedad cardiovascular, aterosclerosis, hipercolesterolemia, enfermedades asociadas con una necesidad de intensificar el transporte reverso de colesterol, enfermedades asociadas con una necesidad de disminuir la absorción del colesterol en el intestino, enfermedades asociadas con una necesidad de incrementar los niveles de colesterol HDL, enfermedades asociadas con una necesidad de reducir los niveles de colesterol LDL; enfermedades inflamatorias, enfermedad de Alzheimer, arteriosclerosis, diabetes tipo 2, afecciones asociadas con una necesidad de mejorar la función HDL; o trastornos lipídicos (dislipidemia) asociados o no con resistencia a la insulina.

25. Un método de tratar y/o prevenir trastornos lipídicos (dislipidemia) asociados o no con resistencia a la insulina; enfermedad cardiovascular, aterosclerosis, hipercolesterolemia, enfermedades asociadas con una necesidad de intensificar el transporte reverso de colesterol, enfermedades asociadas con una necesidad de disminuir la absorción del colesterol en el intestino, enfermedades asociadas con una necesidad de de incrementar los niveles del colesterol HDL, enfermedades asociadas con una necesidad de disminuir los niveles del colesterol LDL; enfermedades inflamatorias, enfermedad de Alzheimer, arteriosclerosis, diabetes tipo 2, o afecciones asociadas con la necesidad de mejora la función HDL, método que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-18, o

su sal apropiada farmacéuticamente aceptable, a un mamífero necesitado de ello.

La presente invención se refiere a ciertos compuestos novedosos de la fórmula (I)



fórmula (I)

a procesos para preparar tales compuestos, a su utilidad en la modulación de receptores hormonales nucleares Receptor X Hepático (LXR)α (NR1H3) y/o β (NR1H2) y en tratar y/o prevenir enfermedades, incluidas enfermedades cardiovasculares tales como aterosclerosis; enfermedades inflamatorias, enfermedad de Alzheimer, trastornos lipídicos (dislipidemias) asociados o no con resistencia a la insulina, diabetes tipo 2 y otras manifestaciones del síndrome metabólico, a métodos para su uso terapéutico y a composiciones farmacéuticas que los contienen.

PCT REQUEST

Original (for **SUBMISSION**)

0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.175)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Swedish Patent Office (RO/SE)
0-7	**Applicant's or agent's file reference**	101613-1 WO
I	**Title of Invention**	NON-ANILINIC DERIVATIVES OF ISOTHIAZOL-3(2H)-ONE 1,1-DIOXIDES AS LIVER X RECEPTOR MODULATORS
II	**Applicant**	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	ASTRAZENECA AB
II-5	Address	151 85 Södertälje Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+46 8 553 260 00
II-9	Facsimile No.	+46 8 553 288 20
III-1	**Applicant and/or Inventor**	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	BROO, Anders
III-1-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-1-6	State of nationality	SE
III-1-7	State of residence	SE

III-2	**Applicant and/or inventor**	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	HOLM, Patrik
III-2-5	Address	Skärgårdsvägen 984 21600 Pargas Finland
III-2-6	State of nationality	FI
III-2-7	State of residence	FI
III-3	**Applicant and/or inventor**	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	JUDKINS, Robert
III-3-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-3-6	State of nationality	GB
III-3-7	State of residence	SE
III-4	**Applicant and/or inventor**	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	LI, Lanna
III-4-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-4-6	State of nationality	SE
III-4-7	State of residence	SE
III-5	**Applicant and/or inventor**	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	LINDSTEDT-ALSTERMARK, Eva-Lotte
III-5-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-5-6	State of nationality	SE
III-5-7	State of residence	SE

III-6	**Applicant and/or inventor**	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	SANDBERG, Pernilla
III-6-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-6-6	State of nationality	SE
III-6-7	State of residence	SE
III-7	**Applicant and/or inventor**	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	SWANSON, Marianne
III-7-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-7-6	State of nationality	SE
III-7-7	State of residence	SE
III-8	**Applicant and/or inventor**	
III-8-1	This person is	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	WEIDOLF, Lars
III-8-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-8-6	State of nationality	SE
III-8-7	State of residence	SE
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	ASTRAZENECA
IV-1-2	Address	Global Intellectual Property 151 85 Södertälje Sweden
IV-1-3	Telephone No.	+46 8 553 260 00
IV-1-4	Facsimile No.	+46 8 553 288 20

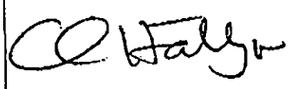
PCT REQUEST

Original (for **SUBMISSION**)

V	**DESIGNATIONS**		
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**		
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	10 January 2005 (10.01.2005)	
VI-1-2	Number	0500055-9	
VI-1-3	Country	SE	
VII-1	**International Searching Authority Chosen**	Swedish Patent Office (ISA/SE)	
VII-2	**Request to use results of earlier search; reference to that search**		
VII-2-1	Date	10 January 2005 (10.01.2005)	
VII-2-2	Number	SE 05/00016	
VII-2-3	Country (or regional Office)	SE	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	272	-
IX-3	Claims	30	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	308	

PCT REQUEST

Original (for **SUBMISSION**)

	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-11	Copy of general power of attorney	reference no. GF 3484/05	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	other	ITS Report SE 05/00016	
IX-19	**Figure of the drawings which should accompany the abstract**		
IX-20	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**		
X-1-1	Name	ASTRAZENECA	
X-1-2	Name of signatory	Christer Hällgren	
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/SE
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

AS: 104 416
1/2

582

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Pais:** Suecia

El presente documento oficial

2. **ha sido firmado por** Anne-Marie Bonde
3. **en su calidad de** Notario Público
4. **y lleva el timbre/sello de**

Notario Público en Estocolmo

Lo cual se certifica

5. **en** Estocolmo
6. **el** 11.07.2007
7. **por** Björn Sandin

Notario Público

8. **No** 2767
9. **Timbre/Sello:**
10. **Firma:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

101613 (0

69

ASSIGNMENT

The undersigned,

Please turn over!

domiciled in
Please turn over!

hereby state under oath to be the sole and true inventor of

NON-ANILINIC DERIVATIVES OF ISOTHIAZOL-3(2H)-ONE 1,1-DIOXIDES AS LIVER X RECEPTOR MODULATORS

We state as well that we assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of Sweden

domiciled in

SE-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Please turn over!

.....

TRASPASO

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

organizada y existente de conformidad con la leyes de

domiciliada en

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

.....

NOTARIUS PUBLICUS i STOCKHOLM
ANNE-MARIE EDNOE

Inventors:

Signature
Name **Anders BROO**
Date 2007-07-06
Nationality SE

Signature
Name **Robert JUDKINS**
Date 2007-06-21
Nationality GB

Signature
Name **Lanna LI**
Date 2007-06-21
Nationality SE

Signature
Name **Eva-Lotte LINDSTEDT-ALSTERMARK**
Date 2007-07-03
Nationality SE

Signature
Name **Pernilla SANDBERG**
Date 200706-20
Nationality SE

Signature
Name **Marianne SWANSON**
Date 2007-07-02
Nationality SE

Signature
Name **Lars WEIDOLF**
Date 2007-07-03
Nationality SE

Signature
Name **Kay BRICKMANN**
Date 20070620
Nationality DE

All the above of: AstraZeneca R & D Mölndal, S-431 83 Mölndal, Sweden

Signature
Name **Patrik HOLM**
Date
Nationality FI

Of: Skärgårdsvägen 984, FIN-21600 Pargas, Finland

Yo, la suscrita, Anne-Marie Bonde, Notario Publico en Estocolmo, Suecia, certifica que ANDERS BROO, ROBERT JUDKINS, LANNA LI, EVA-LOTTE LINDSTEDT-ALSTERMARK, PERNILLA SANDBERG, MARIANNE SWANSON, LARS WEIDOLF y KAY BRICKMANN **han ortogado y firmado el documento que antecede.**

Derechos 550:- **Estocolmo,** 2007-07-11

Coronas **De oficio:**

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

684

ASSIGNMENT

The undersigned,

Please turn over!

TRASPASO

abajo firmado

domiciled in
Please turn over!

domiciliado en

hereby state under oath to be the sole and true inventor of

declara bajo juramento ser único y verdadero inventor de.

NON-ANILINIC DERIVATIVES OF ISOTHIAZOL-3(2H)-ONE 1,1-DIOXIDES AS LIVER X RECEPTOR MODULATORS

We state as well that we assign, without reservations or limitation, in favor of

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

a corporation organized and existing under the laws of Sweden

organizada y existente de conformidad con la leves de

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all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Please turn over!

.....

.....

Inventors:

Signature		Signature	
Name	**Anders BROO**	Name	**Robert JUDKINS**
Date		Date	
Nationality	SE	Nationality	GB
Signature		Signature	
Name	**Lanna LI**	Name	**Eva-Lotte LINDSTEDT-ALSTERMARK**
Date		Date	
Nationality	SE	Nationality	SE
Signature		Signature	
Name	**Pernilla SANDBERG**	Name	**Marianne SWANSON**
Date		Date	
Nationality	SE	Nationality	SE
Signature		Signature	
Name	**Lars WEIDOLF**	Name	**Kay BRICKMANN**
Date		Date	
Nationality	SE	Nationality	DE

All the above of: AstraZeneca R & D Mölndal, S-431 83 Mölndal, Sweden

Signature
Name **Patrik HOLM**
Date
Nationality FI

Of: Skärgårdsvägen 984, FIN-21600 Pargas, Finland

This is to certify the above own hand signature(s)
of PATRIK HOLM
Turku, 13th of July 2007
Ex officio:
Minna Kökkö
Inspector, Notary Public

Turun seudun maistraatti
Magistraten i Åboregionen

6 de

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 2007, compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 2007 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 2007, compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 13th day of July 2007 personally appeared before me, a Notary Public,

MINNA KÖKKÖ

MINNA KÖKKÖ
TARKASTAJA, JULKINEN NOTAARI
INSPEKTÖR, NOTARIUS PUBLICUS

Turun seudun maistraatti
Magistraten i Åboregionen

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

604

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Maa: / Land: — Suomi / Finland

Tämän yleisen asiakirjan: / Denna allmänna handling:

2. on allekirjoittanut / är undertecknad av — Minna Kökkö

3. toimiessaan / i egenskap av — tarkastajana, julkisena notaarina (notarius publicus).

4. Siinä oleva leima/sinetti on / är försedd med sigill/stämpel av — Turun seudun maistraatin leima.

Todistetaan / Intygas

5. Turussa / I Åbo — 6. 13 päivänä heinä kuuta 2007 / den 2007

7. av — Irma Hackman, Turun seudun maistraatin julkinen notaari (notarius publicus)

8. No / Nr T397 /2007

9. Sinetti/Leima: / Sigill/Stämpel



10. Allekirjoitus: / Underskrift

Irma Hackman
Maistraatin päällikkö, julkinen notaari
Chef för Magistraten, notarius publicus
Turku, Finland

TRADUCCIÓN AL ESPAÑOL del documento de cesión otorgado a **ASTRAZENECA AB**, firmado por los Cedentes y el Cesionario.

En el documento de Cesión hay un sello que dice:

Este es para certificar la firma de arriba
de Patrik Holm
Turku 13 de julio de 2007
Ex oficio
Minna Kökkö
Inspector, Notario Público.

APOSTILLA
(Convención de La Haya del 5 de octubre de 1961)

1. País: Finlandia

   Este documento público

2. ha sido firmado por Minna Kökkö

3. actuando en capacidad de Inspector, Notario Público (Notario Público)

4. lleva el sello de Sello de Dirección de Magistrados de Turun

CERTIFICADO

5. en Turun 6. el 13 de julio de 2007

7. por Irma Hackman, Jefe del Magisterio de Notarios Públicos (Notario Público)

8. No. T397 /2007

9. Sello 10. Firma:

(Firma)
Irma Hackman
Jefe del Magisterio de Notarios Públicos
Tuku, Finlandia.

Brigard & Castro

BOGOTA - COLOMBIA

PODER

Yo (nosotros),

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO S.**
de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez; corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lc(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO S.**
domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mi (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domiciled in SE-151 Sodertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or explotation of licenses, action of unfair competition; penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures: and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Macclesfield, Cheshire, England

this 19th day of July 2003

Signature

Name KEVIN BILL

NOTARIA CUARENTA Y SEIS ENCARGADO
DEL DESPACHO DE LA NOTARIA CUARENTA Y SEIS
EL SUSCRITO NOTARIO CONSTATA QUE ESTA COPIA FOTOSTATICA ES IGUAL AL DOCUMENTO PRESENTADO
EL 23 FEB. 2007
ROSA FALLA LAISECA
NOTARIO CUARENTA Y SEIS ENCARGADO

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2007 of
personally appeared before me
KEVIN BILL
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that purpose for which this instrument is granted included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Sweden
under date of 1st January 2007

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron)
ante mí

a quien(es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)

DECIMO NOTARIO CUARENTA Y SEIS ENCARGADO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE COPIA FOTOSTATICA COINCIDE CON EL QUE ME FUE PRESENTADO A LA VISTA D.C. REPUBLICA DE COLOMBIA
23 FEB. 2007
ROSA FALLA LAISECA
NOTARIO CUARENTA Y SEIS ENCARGADO

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

2 6

APOSTILLE

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by **J B Hodgson**
   a été signé par

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

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

Certified/Attesté

5. at London/à Londres

6. the/le **17 February 2004**

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

8. Number/sous No **G348987**

9. Stamp:
   timbre:

10. Signature: **J. Ireland**

FOREIGN AND COMMONWEALTH OFFICE LONDON

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

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

COMO NOTARIO CUARENTA Y [illegible] ENCARGADO DEL CIRCULO DE [illegible] DAGO CONSTAR QUE ESTA COPIA FOTOSTATICA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
D.C. REPUBLICA DE [illegible]
23 FEB. 2007
ROSA FALLA LAISECA
NOTARIO CUARENTA Y [illegible] ENCARGADO

6 41

TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el **Poder** concedido por **ASTRAZENECA AB**, domiciliada en SE - 151 Sodertalje, Suecia a **Ramiro Castro Duque** y/o **Juan Pablo Cadena Sarmiento** y/o **Beatriz Jaramillo S**, domiciliados en la Carrera 7 #16-56, P. 9, Bogotá D.C., Colombia.

AUTENTICACIÓN

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

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
   ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

CERTIFICADO

5. en Londres 6. el **17 de Febrero de 2004**
7. por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello 10. Firma

J. Ireland (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país.

COMO NOTARIO CUARENTA Y SUS ENCARGADO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
D.C. REPUBLICA DE COLOMBIA
23 FEB. 2007
ROSA FALLA LAISECA
NOTARIO CUARENTA Y SUS ENCARGADO

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REPÚBLICA DE COLOMBIA

GAVIRIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

Datos de la oficina de registro

Clase de oficina: Registraduría [ ] Notaría [X] Consulado [ ] Corregimiento [ ] Insp. de Policía [ ] Código 9790

País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C. NOTARIA 32

Datos del fallecido

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)

C.C. No. 170322 DE BOGOTA

Sexo (en letras)

MASCULINO

Datos de la defunción

Lugar de la Defunción País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción: Año 2004 Mes 10 Día 30

Hora: 04:10 PM

Número de certificado de defunción: A-- 2094375

Presunción de muerte

Juzgado que profirió la sentencia

Fecha de la sentencia: Año Mes Día

Documento presentado

Autorización judicial [ ] Certificado Médico [X]

Nombre y cargo del funcionario

ANDRES DIAZ CAMPOS
R.M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO H.

Documentos de Identificación (Clase y número)

C.C. No. 15.030.154 DE LORICA/ CORDOBA

Firma

Primer testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)

Firma

Segundo testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)

Firma

Fecha de inscripción

Año 2004 Mes 1 Día 02

Nombre y firma del funcionario que autoriza

BLANCA NIDIA LONDOÑO RESTREPO
NOTARIA 32

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO QUE:

La presente acta es Fiel copia del original tomada del registro civil de defunciones serial indicativo número: 5762291
que expedido en la ciudad de Bogotá D.C. hoy: 05 NOV. 2004

NOTARIA 32
SECRETARIO DELEGADO

NELSON FLOREZ G.
SECRETARIO DELEGADO PARA COTEJAR
DECRETO 1334 DE 1986

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-081262- -00000-0000

Fecha: 2007-08-09 15:59:49 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 692

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Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de 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 [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica 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 [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

_____
Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Nota: El expediente no se encuentra correctamente foliado.
El número real de folios es 706

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 708

2020
Bogotá D.C.,

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA		
	Radicación No.	7 81262
	Solicitud internacional	PCT/SE2006/000029
	Fecha inicio fase nacional	10/08/2007
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	4024
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 02 OCT. 2007

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

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