Industria y Comercio

SUPERINTENDENCIA

P C T

Delegatura de propiedad Industrial

División de Nuevas Creaciones

06-95141 S.S.

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-95141

54. **TÍTULO** Piperazinas Derivadas de Urea para el tratamiento de la Endometrosis

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** Schering Aktiengesellschaft

DOMICILIO Mullerstrasse 178, 13353, Berlin, Aleman

74. **APODERADO** J. IAN. Raisbeck

22. **BOGOTÁ, D. C.,** 21 de septiembre del 2006

(FORMA P-10)

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-095141- -00000-0000 -
Fec 2006-09-21 16 47:35 Dep 2020 NUEVCREACIONES
Tra 11 -PATENTEIYII
Eve 379 FASENACIONALII

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 29-09-06

(1) **SOLICITUD DE:**

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

[ ] Capítulo I. [X] Capítulo II.

(2) **S LICITANTE (71)**

Nombre: SCHERING AKTIENGESELLSCHAFT
Dirección: Mullerstrasse 178, 13353, Berlin Alemania
Nacionalidad o Domicilio: ALEMANA
Lugar de Constitución: ALEMANIA
Teléfono: Fax:
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) **REPRESENTANTE O APODERADO**

Nombre: J. IAN RAISBECK
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 Fax: 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.376.996 Btá
TP 135.799

(4) **INVENTOR (ES) (72)**

Nombre: RICHARD HORUK, ULRIKE KAUFMANN
Dirección: 3410 Silver Springs Court, Lafayette, California CA 94549, E.U.A. y Dorotheenstrasse 56, 10117, Berlin, Alemania;
Nacionalidad o Domicilio: ESTADOUNIDENSE, ALEMANA

(5) **PCT (86)**
Solicitud Internacional No. PCT/EP2005/002036 Fecha Febrero 23, 2005
Publicación Internacional No. WO 2005/079769 Fecha Septiembre 1, 2005

(6) **Título (54):** PIPERAZINAS DERIVADAS DE UREA PARA EL TRATAMIENTO DE LA ENDOMETROSIS

(7) **Clasificación Internacional (51)** A61K 31/00

(8) **Prioridad**
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Febrero 24, 2004	04090065.6

(9) **Comprobante de pago No.** 06 – 72,730 **Fecha** Septiembre 20, 2006

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso Ver expediente No. 05-119.657. Adjunto copia simple.
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [x] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [x] Otros Búsqueda Internacional

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-095141- -00000-0000
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Tra. 11 PATENTES Y M
Ese 379 FASE NACIONAL II

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 72,730
FECHA : SEPTIEMBRE 20 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECR	CONSIGNACION	BANCO POPULAR	050-00110-6	52198850	20/09/2006	4,848,000.00

C O N C E P T O

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

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

N 004947041

FOLIO 189.- PRIMERA COPIA.- ESCRITURA NÚMERO: CUARENTA Y CINCO.- SUSTITUCIÓN PARCIAL DE PODER: MESSERER, Gerardo a favor de OLARTE, Carlos Reinaldo y otro.- En la Ciudad Autónoma de Buenos Aires, Capital de la República Argentina, el día **VEINTITRES** de **JUNIO** del año **DOS MIL CINCO**, ante mí María Silvina Lasarte, Escribana Autorizante, titular del Registro Notarial número 1788, **COMPARECE: Gerardo MESSERER**, argentino, mayor de edad, casado en primeras nupcias con Karina Ana Reynolds, titular del Documento Nacional de Identidad número 13 782.654, con domicilio especial en la Avenida Leandro N Alem 1.134, Piso 10°, de esta Ciudad, persona capaz y de mi conocimiento personal, doy fe - **INTERVIENE:** por su propio derecho - **Y EXPRESA: PRIMERO:** Que la Sociedad **"SCHERING AKTIENGESELLSCHAFT"**, con domicilio en Mullerstraße 178, 13353 Berlín, Alemania, le confirió el día 7 de Abril de 2 005 en dicho país, un Poder, el cual mediante escritura número 44, de fecha 22 de Junio de 2.005. otorgada ante mí, al folio 186, protocolo corriente, de este Registro Notarial a mi cargo, fue incorporado y trascripto al mismo, cuya primera copia tengo para este acto a la vista, doy fe y en lo pertinente transcribiré en la presente - **SEGUNDO:** Manifiesta bajo juramento que el referido poder invocado se encuentra plenamente vigente en virtud de no haberle sido revocado, suspendido ni limitado en ninguna de sus partes.- **TERCERO** En consecuencia **DICE:** Que en uso de la facultad conferida **SUSTITUYE PARCIALMENTE** el poder mencionado a favor de **CARLOS REINALDO OLARTE y/o JAMES IAN RAISBECK**, al solo y único objeto de que en nombre y representación de la Sociedad **"SCHERING AKTIENGESELLSCHAFT"** y actuando en forma individual, indistinta y/o alternadamente, se presenten **exclusivamente** ante las autoridades de **COLOMBIA** que correspondan y realicen los

actos enumerados en el citado poder y con las facultades que surgen del mismo, el que transcripto en lo pertinente dice "FOLIO 186 - PRIMERA COPIA - ESCRITURA NÚMERO CUARENTA Y CUATRO - - En la Ciudad Autónoma de Buenos Aires, Capital de la República Argentina, el día VEINTIDÓS de JUNIO del año DOS MIL CINCO, ante mí , Escribana Autorizante, , COMPARECE Gerardo MESSERER, argentino, mayor de edad, casado en primeras nupcias con Karina Ana Reynolds, titular del Documento Nacional de Identidad número 13 782 654, con domicilio especial en la Avenida Leandro N. Alem 1 134, Piso 10°, de esta Ciudad, persona capaz y de mi conocimiento personal, doy fe - INTERVIENE por su propio derecho Y EXPRESA. Que a los efectos que hubiere lugar, solicita de mí, la Autorizante, LA INCORPORACIÓN y TRANSCRIPCIÓN en este protocolo, del PODER que le fuera conferido a su favor el día 7 de abril de 2 005, en Berlín, Alemania, por la Sociedad "SCHERING AKTIENGESELLSCHAFT", con domicilio en Mullerstraße 178, 13353 Berlín, Alemania, sobre cuya plena vigencia responde el requirente bajo juramento - Yo, la Autorizante, hago constar: a) Que el instrumento de poder cuya incorporación y transcripción a este protocolo solicita el compareciente, se encuentra extendido en idioma castellano, certificadas las firmas por notario en idioma alemán, legalizado en idioma alemán (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 1961) y traducido en lo pertinente al idioma nacional por la Traductora Pública Laura Thieberger - b) Que el requirente tiene interés legítimo en su solicitud - En consecuencia, me hace entrega en este acto del original del instrumento de poder relacionado con su respectiva traducción al idioma nacional, el que agrego a la presente y transcripto dice "MOELLER & CO (sigue texto en idioma extranjero) - Poder Los abajo firmante/s Schering Aktiengesellschaft Mullerstraße 178 13353 Berlin, Germany domiciliados en declaran por el presente otorgar a

COLEGIO DE ESCRIBANOS CIUDAD DE BUENOS AIRES CAPITAL DE LA REPUBLICA ARGENTINA

ESCRIBANA MARIA SILVINA LASARTE MATR. 4443

N 004947042

GERARDO MESSERER poder general amplio y suficiente para recabar de las autoridades , sud y centroamericanas . que correspondan, la obtención de patentes de invención, el registro y la renovación de marcas y modelos y/o derechos de propiedad intelectual y/o nombres de dominio, a cuyo efecto lo faculta para llevar a cabo ante dichas autoridades todas las gestiones necesarias al objeto indicado, presentar solicitudes, formular descripciones, oposiciones, protestos, declaraciones, apelaciones y reclamos, oblar impuestos, justificar explotaciones, solicitar testimonios, aceptar transferencias, recibir documentos y valores, percibir y hacer cuanto fuere necesario ante las autoridades administrativas de cualquier orden Por otra parte, le confiere mandato para que en su nombre y representación puedan iniciar y proseguir cualquier juicio que actualmente los que suscriben tengan o en el futuro tuvieran en , en Sudamerica, Centroamérica ., con motivo de su nombre, marcas de fábrica o de comercio, patentes de invención y modelos y/o de sus derechos de propiedad intelectual que actualmente posean o adquieran en lo sucesivo, promover juicios de cualquier jurisdicción, criminales, correccionales, civiles o comerciales, contra los falsificadores, usurpadores o imitadores y contra los tenedores de artículos que infrinjan su nombre, marcas o patentes de invención, seguir los juicios por oposición u otros en que fueran parte como actores o demandados, defender el nombre, las marcas, patentes y modelos y/o de derechos de propiedad intelectual y/o nombres de dominio, haciendo las protestas del caso o diciendo de nulidad Al efecto, podrá presentarse con escritos, querellas, pedidos, y lo que fuere necesario ante cualquier autoridad judicial, presentar testigos, documentos y demás justificativos, rendir pruebas de cualquier especie, pedir nombramientos de peritos, pedir y absolver posiciones, asistir a juicios verbales, declinar y prorrogar de jurisdiccion, tachar, recusar, apelar, transar, someter a arbitraje o mediación, hacer renuncias, exigir y dar

cauciones, pedir embargos preventivos, definitivos o inhibiciones y su levantamiento, pedir la venta de los bienes de los deudores, solicitar y obtener el cumplimiento de sentencias, prestar juramentos, decir de nulidad, desistir, percibir, otorgar recibos y en general practicar todos los actos y diligencias que sean precisos al desempeño de este mandato Podrá asimismo substituir el presente poder en todo o en parte. Dado y firmado en Berlin, 2005-04-07 Schering Aktiengesellschaft Corporate Patents ppa. ppa Hay dos firmas ilegibles Dr Thomas Seuß Dr Walter Klose" - ES COPIA FIEL, doy fe - En hoja adjunta consta la certificación notarial de las firmas obrantes en el poder, en idioma alemán, efectuada por el Notario de Alemania, Dimitri Rempen y en hoja siguiente consta la legalización de la firma y sello del mencionado notario, en idioma alemán (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 1961) doy fe - A continuación sigue la referida traducción de lo pertinente al idioma nacional la que transcripta textualmente dice "TRADUCCION PUBLICA (A continuación de un PODER otorgado en idioma nacional por la Sociedad "Schering Aktiengesellschaft", de Berlín, Alemania, redactado en idioma nacional, aparecen los siguientes textos que traducidos dicen) - La versión en inglés es para su información únicamente - Registro de Actas N° R 142/2005 - He advertido sobre la prohibición de colaboración según el Artículo 3, Párrafo 1, N° 7, de la Ley de Certificaciones. Mi pregunta de que si existe alguna disposición previa en el sentido de dicha Norma, fue contestada negativamente - Certifico la autenticidad de las firmas trazadas ante mí por los siguientes - Dr Walter Klose, que nació el 26 de diciembre de 1952, y del Dr Thomas Seuss, que nació el 17 de setiembre de 1963, ambos de mi personal conocimiento- ambos con domicilio comercial en 13353 Berlín, Mullerstrasse 178 - Al mismo tiempo doy fe, en base a que tuve a la vista en el día de hoy las Actas del Registro de Comercio del Tribunal de Primera Instancia de Charlottenburg, N° de

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N 004947043

Acta HR B 283, que el Dr Klose y el Dr Seuss están autorizados en su carácter de Mandatarios a representar a la Sociedad "Schering Aktiengesellschaft' de Berlín - Berlín, 7 de abril de 2005.- (Firma ilegible del Escribano, liquidación de derechos y sello en oblea aplicado sobre precinto) TRIBUNAL DE PRIMERA INSTANCIA DE CHARLOTTENBURG - BERLÍN - APOSTILLA- (Convención de La Haya del 5 de octubre de 1961)- País. República Federal de Alemania - Este Instrumento público fue firmado por Dimitri Reinpen, actuando en carácter de Escribano y lleva el sello del Escribano -Certificado en Berlín, el 28 de abril de 2005 por el Presidente del Tribunal Regional de Berlín con el Nº 9101 a E- F 1927/2005 – Sello (Hay un sello en oblea sobre precinto) PRESIDENTE DEL TRIBUNAL REGIONAL DE BERLIN– El Funcionario autorizado (Firmado y aclarado) Bünning – Juez Principal del Tribunal Regional - ES TRADUCCION FIEL de las partes pertinentes del documento de referencia, que en los idiomas alemán e inglés, he tenido y he vertido al idioma nacional, en Buenos Aires, el 19 de mayo de 2005 - Hay una firma ilegible y un sello que dice. "Laura Thieberger Matrícula de Traductores. Alemán- Francés Tomo II Folio 254 (Cap) Tomo III - 98- (La Plata) Inglés. Tomo III - Folio 14 (Cap) Tomo III - Folio 329 (La Plata) Colegio Traductores Públicos Nº 173 " - ES COPIA FIEL, doy fe - A continuación hay un sello que dice "COLEGIO DE TRADUCTORES PUBLICOS DE LA CIUDAD DE BUENOS AIRES Corresponde a la Legalización Nº T5-3258/05 Hay una firma ilegible y aclarada Gustavo Adrián SIGALOFF" - En el margen superior derecho hay un sello timbrador que dice "COLEGIO DE TRADUCTORES PÚBLICOS 24 5 05 LEGALIZACIONES $20 00 CTPBA. UNIDAD Nº 2 " A continuación sigue la legalización de la firma de la nombrada traductora, , que dice "Nº 00824188 COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES República Argentina Ley 20 305

N 004947043

LEGALIZACIÓN Por la presente el COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES, en virtud de la facultad que le confiere el artículo 10, inc. d) de la Ley 20.305, certifica únicamente que la firma y sello que aparecen en la traducción adjunta, concuerdan con los correspondientes al Traductor Publico THIEBERGER, LAURA que obran en los registros de esta institución en el folio tomo ALEMAN 254 2 INGLES 14 3 Buenos Aires, Legalización Número 3258/2005/T5 Fecha 24/05/05 - Hay una firma ilegible. Hay un sello que dice Marcelo F Sigaloff Encargado Dto de Legalizaciones Colegio de Traductores Públicos de la Ciudad de Buenos Aires - ES COPIA FIEL, doy fe - En este estado el compareciente expresa que en la forma expresada deja INCORPORADO y TRANSCRIPTO en este Protocolo el Poder que agrego a la presente, solicitando de mí, la Escribana Autorizante, expida primera copia de la presente para el nombrado apoderado -. . - LEO esta escritura al compareciente, quien así la otorga y en prueba de conformidad, la firma ante mí, doy fe - GERARDO MESSERER Ante mí MARIA SILVINA LASARTE Escribana. Está mi sello CONCUERDA con su escritura matriz que pasó ante mí, al folio 186 del Registro Notarial número 1788, a mi cargo PARA EL APODERADO expido la presente PRIMERA COPIA en tres (3) sellos de actuación notarial numerados correlativamente desde el número N004823958 al presente inclusive, que sello y firmo en la fecha y lugar de su otorgamiento, doy fe " Sigue una firma y un sello María Silvina Lasarte Escribana Mat 4413 " - **ES COPIA FIEL**, de las partes pertinentes de la escritura de referencia, doy fe - **CUARTO**. Finalmente el compareciente expresa a) Que el presente otorgamiento no significa renunciar al ejercicio de las facultades sustituidas, y b) Que los nombrados apoderados sustitutos NO podrán sustituir el presente poder en ninguna de sus partes - Yo, la Autorizante advierto al compareciente, a tenor de lo dispuesto en

N 004947044

el artículo 77 inciso h) de la Ley Orgánica Notarial Número 404, respecto de los alcances de las cláusulas contenidas en la presente escritura y del derecho de leer por sí este instrumento - **LEO** esta escritura al compareciente, quien así la otorga y en prueba de conformidad la firma ante mí, doy fe - GERARDO MESSERER Ante mí. MARIA SILVINA LASARTE Escribana Está mi sello **CONCUERDA** con su escritura matriz que pasó ante mí, al folio 189 del Registro Notarial número 1788, a mi cargo. PARA EL PODERDANTE expido la presente **PRIMERA COPIA** en cuatro (4) sellos de actuación notarial numerados correlativamente desde el número N004947041 al presente inclusive, que sello y firmo en la fecha y lugar de su otorgamiento, doy fe -

CECBA - LEY404 GCBA
LEGALIZACION
050623226358
$20 00
23/06/2005 14 48 41

CECBA - LEY404 GCBA
APOSTILLA
050623035431
$39 00
23/06/2005 14.48 49

COLEGIO DE ESCRIBANOS

N 004947044

CES de la BUFI

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00037959

1 País REPUBLICA ARGENTINA

El presente documento publico

2 Ha sido firmado por NESTOR ESTEBAN AZLOR

3 Quien actúa en calidad de LEGALIZADOR

4 Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

5 En LA CIUDAD DE BUENOS AIRES 6 El día 23/06/2005

7 Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8 Bajo el número. 050623035431

9 Sello / Timbre

10 Firma

8

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL REPUBLICA ARGENTINA

LEGALIZACIÓN

1 006549485

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente LEGALIZA la firma y sello del escribano MARIA SILVINA LASARTE

obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº 050623226358/6 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Jueves 23 de Junio de 2005

ESC. NESTOR ESTEBAN AZLOR
COLEGIO DE ESCRIBANOS
LEGALIZADOR

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

(19) World Intellectual Property Organization
International Bureau

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04090065 6 24 February 2004 (24 02 2004) EP

(71) Applicants (*for all designated States except US*): SCHERING AKTIENGESELLSCHAFT [DE/DE], Müllerstrasse 178, 13353 Berlin (DE) HORUK, Richard [US/US], 3410 Silver Springs Court, Lafayette, CA 94549, California CA 94549 (US)

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): KAUFMANN, Ulrike [DE/DE], Dorotheenstr 56, 10117 Berlin (DE)

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

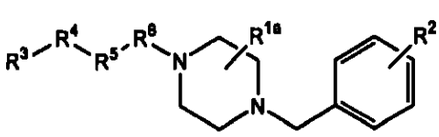
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, 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:
— *without international search report and to be republished upon receipt of that 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

WO 2005/079769 A2

(54) Title: PIPERAZINE UREA DERIVATIVES FOR THE TREATMENT OF ENDOMETRIOSIS



(Ia)

(57) Abstract: Use of a compound of the following formula (Ia) for the production of a medicament for the treatment of endometriosis in human wherein the treatment comprises administering to a human female in need of such treatment a therapeutically effective amount of said compound

PIPERAZINE UREA DERIVATIVES FOR THE TREATMENT OF ENDOMETRIOSIS

DESCRIPTION

Field of the Invention

The present invention is directed to piperazine derivatives and their pharmaceutically acceptable salts, which inhibit the activity of the chemokines, MIP-1α and RANTES being antagonists of Human Chemokine "C-C" receptor 1 (CCR1) thereby being useful for the treatment of endometriosis It also relates to pharmaceutical compositions containing the derivatives or their pharmaceutically acceptable salts, and methods of their use

BACKGROUND OF THE INVENTION

Chemokine receptors are expressed on leukocytes and process the signals following the binding of the chemokine whereby such signals are eventually transduced into migration or activation of the leukocytes towards the source of the chemokine. Therefore, by regulating the migration and activation of leukocytes from the peripheral blood to extravascular sites in organs, skin, articulations or connective, tissue, chemokines play a critical role in the maintenance of host defense as well as in the development of the immune response

Human Chemokine "C-C" receptor 1 (CCR1) has been shown to respond to a number of human CC chemokines in a variety of assays including calcium mobilization, inhibition of adenylyl cyclase increase in extracellular acidification and chemotaxis. The range of chemokines that can signal through CCR1 is broad and includes MIP-1 alpha, RANTES, MCP-3, amongst others All of these ligands are potent agonists for human CCR1 (EC50's < 10 nM) In addition, human CCR1 is also able to bind human MIP-1ß and MCP-1 with low affinity (>100 nM) but neither ligand is able to signal (1) Using polyclonal antibodies to CCR1 the receptor has been shown to be expressed in monocytes, and lymphocytes but not in neutrophils (2)

Molecules inhibiting the activity of CCR1 have been reported to be beneficial in treating diseases such as multiple sclerosis, rheumatoid arthritis and other chronic inflammatory diseases

Endometriosis is a chronic inflammatory disease, characterized by implantation and growth of endometrial tissue outside the uterine cavity (3). It is classically described as the presence of endometrial tissue (glandular epithelium and stroma) outside the

uterine cavity Endometriosis is a benign chronic disease, that affects 15–20% of all women in their reproductive life.

The symptoms of endometriosis are chronic pelvic pain, progressive dysmenorrhea, dyspareunia as well as infertility

The treatment of endometriosis involves surgical resection and / or medication with hormonal agents such as gonadotropin-releasing hormone (GnRH) agonists and androgens However, long-term medication with hormonal agents is undesirable because of side effects such as menopausal disorders (hot flushes), genital bleeding and bone demineralization

The clinical control of endometriosis is often very difficult and the recurrence rate is high after discontinuation of medication.

The role of CCR1 and its ligands in endometriosis arises from the fact that retrograde menstruation is postulated as the initiating event in the pathogenesis of the disease. Furthermore, this is accompanied by an intraperitonial infiltration of macrophages and T cells in endometriotic lesions. The recruitment of these leukocytes into the endometrial lesions is initiated by the local production of chemokines the most notable example the CC chemokine RANTES (3-7), which is, amongst others, a ligand for the chemokine receptors CCR1, and CCR5 . The expression of RANTES is up-regulated in endometriotic lesions and in peritoneal fluid from patients with endometriosis. In comparison to other chemokines, RANTES plays an important role in the pathogenessis of endometriosis.

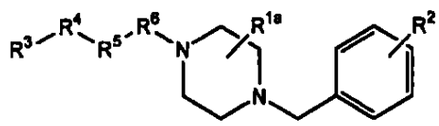
Related Disclosures

Piperazine derivatives of the type similar to the compounds of the invention are known in the literature as being useful for a variety of pharmaceutical indications, particularly as cardiotonic, neurotropic or anti- inflammatory agents For example, published European Patent Application 0 702 010 (Adir) describes certain piperazine derivatives as being useful as central nervous system depressants and in the treatment of Alzheimer's and other diseases of immunological origin, such as arthritis and intestinal peristaltism Published European Patent Application 0 655 442 (Fujisawa) describes similar piperazine derivatives as tachykinin antagonists useful in treating inflammatory diseases such as rheumatoid arthritis and osteoarthritis A Czech published patent application. 260089, and related article, Valenta, V *et al.*, *Collection Czechoslovak Chem. Commun.* (1987), Vol 52, pp 3013-3023, disclose piperazine derivatives as potential neurotropic and cardiovascular agents European Published Patent Application 0 252 422 (Mitsubishi) and German Published Patent Application 3614363

(Hoechst) describe piperazine derivatives as being useful as cardiotonic agents
European Published Patent Application 0 190 685 (G D Searle) describes piperazine derivatives which block the 5- lipoxygenase pathway of the arachidonic acid cascade, thereby being useful in the treatment of allergic and hypersensitivity reactions and inflammation PCT Published Patent Application, WO 96/34864 (Schering Plough) discloses piperazine derivatives useful as neurokinin antagonists.
European Published Patent Application 1 254 899 (Schering AG) discloses the piperazine derivatives comprised in the present application for the treatment of an inflammatory disorder
PCT patent application WO02/36581 (Schering AG) discloses also piperazine derivatives comprised in the present application for the diagnosing Alzheimer's disease
All of the above references are incorporated herein in full by reference.
None of the above references describe the piperazine derivatives comprised in the present application for the treatment of endometriosis in human females, said piperazine derivatives being antagonists of Human Chemokine "C-C" receptor 1 (CCR1)

SUMMARY OF THE INVENTION

This invention is directed to the use of a compound of the following formula (Ia) or its pharmaceutically acceptable salt for the treatment and prevention of edometriosis in human wherein the treatment comprises administering to a human female in need of such treatment a therapeutically effective amount of said compound.
Accordingly, in one aspect, this invention provides compounds of the following formula (Ia)



(Ia)

wherein:
R^{1a} is
one or more substituents independently selected from the group consisting of oxo, halo, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, formyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl,

alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkylthioalkyl, aminoalkyl monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, azidoalkyl, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, (alkoxycarbonylalkyl) ureidoalkyl, alkoxycarbonylaminoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, alkoxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, aralkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, arylsulfonyl, heterocyclyl and heterocyclylalkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hyaroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl) (alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino,

ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl,

R^3 is

a carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, arylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, hydroxyalkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, aminoalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy) cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy) aralkyl, (monoalkylamino) aralkyl, (hydroxyalkyl)hioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkylamino, heterocyclylamino, (cycloalkylalkyl)amino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl) aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, (hydroxyalkoxy)carbonyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, dialkylaminocarbonyloxyalkyl, alkylcarbonylalkyl, arylcarbonylalkyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, (aminocarbonylalkyl) aminocarbonyl, (monoalkylaminocarbonylalkyl) aminocarbonyl, (carboxyalkyl) aminocarbonyl, (alkoxycarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino,

hydroxyamidino, guanidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, monohaloalkylureido, (monoalkyl)(monoaryl)ureido, dialkylureido, diarylureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl) ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl) glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, glycinamidoalkyl, alaninamido, monoalkylalaninamido, alaninamidoalkyl, heterocyclyl and heterocyclylalkyl,

or R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkylsufonyl, arylsulfonyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, haloalkoxy, alkenyl, alkynyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl) aminoalkyl, alkoxycarbonylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, guanidino, ureido, monoalkylureido, ureidoalkyl, monoalkylureidoalkyl, and glycinamido;

R^4 is

-O-, $-N(R^7)-$, $-C(R^8)_2-$ or a bond,

R^5 is

an alkylene chain or an alkylidene chain, or, if R^4 is a bond, R^5 is an alkylidene chain optionally substituted by aryl or $-N(R^7)_2$;

or R^4 and R^5 together are a -CH=CH-

R^6 is

-C(O)-, - C(S)-, $-CH_2-$ or a bond;

each R^7

is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl, and

each R^8

is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl) (alkyl)amino, aralkylcarbonylamino, (aralkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, aralkylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, (aralkylcarbonyl)(alkyl)aminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, and dialkylaminocarbonylalkyl;

provided that when R^4 is $-N(R^7)-$, R^3 can not be a heterocyclic ring system containing 4-8 members consisting of carbon atoms and only one nitrogen atom, and provided that when R^4 is $-C(R^8)_2$ or a bond, R^3 can not be a bridged saturated heterocyclic ring system containing 4-6 members consisting of carbon atoms and two nitrogen atoms, and as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof The provisio was made to exclude compounds disclosed in prior art document WO 96/34864

The patent application WO2004/037796 in its entireties is hereby incorporated by reference to the present application Advantageous forms of embodiment according to the present invention are the compound according to the general formula I, II, IIa and III as defined in WO2004/037796 for the production of a medicament for the treatment

and prevention of edometriosis Particularly favourable embodiments of the present invention are the following compounds as reported in WO2004/037796

(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oXopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oxopropenyl] phenyl)-methanesulfonamide,

(5-Chloro-2-[(E)-3-[(2R, 5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-methanesulfonamide,

(5-Chloro-2- {(E)-3-[4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-phenyl)-acetic acid methyl ester,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-benzoic acid,

(5-chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-urea,

(5-Chloro-2-{(E)-3-{(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxopropenyl}-4-trifluoromethoxy-phenyl)-urea,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oXo-propenyl}-4-methoxy-benzoic acid methyl ester

The patent application WO03/035627 in its entireties is hereby incorporated by reference to the present application Advantageous forms of embodiment according to the present invention are the compounds under the general formula 1 as defined in claim 1 of WO03/035627 for the treatment and prevention of edometriosis Particularly favourable embodiments of the present invention are the following compounds as reported in WO03/035627.

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-propionic acid,

(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4- (4-chloro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(3, 4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acrylic acid,

N-[(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-methanesulfonamide,

N- (5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzoyl)-methanesulfonamide,

N- [(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-C,C,C-trifluoro-methanesulfonamide,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-oxo-acetic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-acetic acid,

2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-2-methyl-propionic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-difluoro-acetic acid

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide

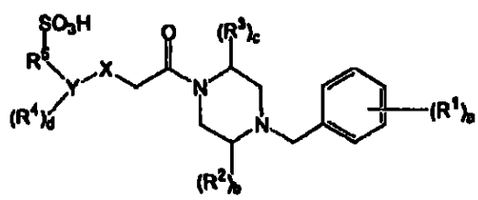
The patent application WO01/72728 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds under the general formula 1 as defined in page 2 of WO01/72728 as pablished for the treatment and prevention of edometriosis

Particularly favourable embodiments of the present invention are the following compounds as reported in WO01/72728:

N-[5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]phenyl-trifluoromethanesulfonamide,

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]- benzenesulfonamide

The patent application WO02/102787 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds of the formula I- WO02/102787



(I- WO02/102787)

or the pharmaceutical acceptable salts and prodrugs thereof; wherein

a = 0, 1, 2, 3, 4 or 5, b = 0, 1 or 2; c = 0, 1 or 2, d = 0, 1,2, 3 or 4,

X is -O-, -S-, -CH2- or -NR6-

Y is(C6-C10) aryl, or(C2-C9) heteroaryl,

each R1 is independently selected from the group consisting of: H-, HO-, halo-, (C1-C8) alkyl- optionally substituted with 1-3 fluorine atoms, (C1-C8) alkyl-O- wherein the alkyl group is optionally substituted with 1-3 fluorine atoms, HO-(C1-C8) alkyl-, NC-,H2N-, H2N-(C1-C8) alkyl-, HO-(C=O)-, (C1-C8)alkyl-(C=O)-, (C1-C8)alkyl-(C=O)-(C1-C8)alkyl-, H2N-(C=O)-, H2(C=O)-(C1-C8) alkyl-,

each R2 and R3 is independently selected from the group consisting of H-, oxo, (C1-C8) alkyl- optionally substituted with 1-3 fluorine atoms, (C1-C8) alkyl-, (C6-C10) aryl-, (C6-C10)aryl-(C1-C8)alkyl-, HO-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C1-C8)alkyl, H2N-(C1-C8)alkyl, (C1-C8)alkyl-NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C2-C9)heterocyclyl-(C1-C8)alkyl, (C1-C8)alkyl-(C=O)-NH-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C=O)-NH-(C1-C8)alkyl, H2N-

(C=ONH-(C1-C8)alkyl, (C1-C8)alkyl-SO2-NH-(C1-C8)alkyl, (C2-C9)heteroaryl-(C1-C8)alkyl, H2N-(C=O)-,H2N- (C=O)- (Cl-C8) alkyl-;

each R4 is independently selected from the group consisting of: H-, HO-, halo-, NC-, HO-(C=O-, H2N-, (C1-C8)alkyl-NH-, [(C1-C8)alkyl]2N-, (C1-C8)alkyl- optionally substituted with 1-3 fluorine atoms,(C1-C8) alkyl-O- wherein the alkyl group is optionally substituted with 1-3 fluorine atoms, HO-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C1-C8)alkyl-, H2N-(C1-C8)alkyl-, (C1-C8)alkyl NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C1-C8)alkyl-(C=O)-, (C1-C8)alkyl-(C=O)-(CC8) alkyl-, (C6-C10)aryl-, (C2-Cg) heteroaryl-, (C6-C10) aryloxy, H2N-(C=O), H2N-(C=O)-(CC8) alkyl, (C1-C8)alkyl-NH-(C=O)-, (C1-C8)alkyl-NH-(C=O)-(C1-C8)alkyl-, [(C1-C8)alkyl]2N (C=O)-, [(C1-C8)alkyl]2-N-(C=O)-(C1-C8)alkyl-, (C3-C8)cycloalkyl-, (C1-C8)alkyl-SO2-, NC-(C C8)alkyl-, (C1-C8) alkyl-(C=O)-NH-, H2N-(C=O)-NH-, H2N-(C=O)-NH-(C1-C8) alkyl-,

R5 is (C1-C8) alkyl-

for the treatment and prevention of edometriosis

Particularly favourable embodiments of the present invention are the following compounds as reported in WO01/72728.

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

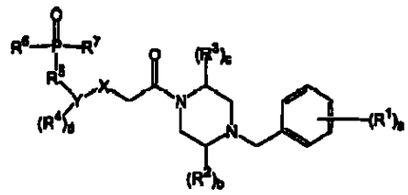
(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

The patent application WO2004/055031 in its entireties is hereby incorporated by reference to the present application Advantageous forms of embodiment according to the present invention are the compounds of the formula I- WO2004/055031



(I-WO2004/055031)

a prodrug thereof, or a pharmaceutical acceptable salt of the compound or the prodrug thereof, wherein

a = 0, 1, 2, 3, 4 or 5, b = 0, 1 or 2; c = 0, 1 or 2, d = 0, 1,2, 3 or 4;

X is O, S, CH2 or NR6;

Y is (C6-C10) aryl or(C2-C9) heteroaryl ;

each R1 is independently. hydroxy, halo,(C1-C8) alkyl optionally substituted with 1 to 3 fluorine atoms,(C1-C8) alkoxy optionally substituted with 1-3 fluorine atoms, HO(C1-C8) alkyl-, cyano, amino, H2N (C1-C8) alkyl-, carboxy,acyl, (C1-C8) alkyl(C=O)(C1-C8)alkyl-, H2N(C=O)-, or H2N (C=O)(C1-C8) alkyl-,

each R2 and R3 are independently oxo,(C1-C8) alkyl optionally substituted with 1-3 fluorine atoms, (C3-C8) cycloalkyl-, (C3-C8)cycloalkyl-(C1-C8)alkyl-, (C6-C10) aryl-, (C6-C10) aryl(C1-C8)alkyl-, HO(C1-C8) alkyl-,(C1-C8) alkyl-O-(C1-C8)alkyl-, H2N(C1-C8) alkyl-, (C1-C8)alkyl-NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C2-C9) heterocyclyl(C1-C8)alkyl-, (C1-C8)alkyl(C=O) NH(Ci-C8) alkyl-, (C1-C8)alkyl-O-(C=O) NH (C1-C8) alkyl-, H2N(C=O) NH(C1-C8) alkyl-, (C1-C8)alkyl-SO2-NH(C1-C8)alkyl-, (C2- C9) heteroaryl(C1-C8) alkyl-, H2N (C=O), or H2N (C=O) (C1-C8)alkyl-,

each R4 is independently HO-,halo-, NC-, HO(C=O)-, H2N-, (C1-C8)alkyl NH-, [(C1-C8)alkyl] 2N-,(Ci-C8) alkyl-, optionally substituted with 1-3 fluorine atoms, (C1-C8) alkoxy optionally substituted with 1-3 fluorine atoms, HO (C1-C8) alkyl-, (C1-C8) alkyl-O-(C1-C8)alkyl-, H2N(C1-C8)alkyl–, (C1-C8)alkylNH(C1-C8)alkyl-, [(C1-C8)alkyl] 2N (C1- C8) alkyl-, (C1-C8)alkyl(C=O)-, (C1-C8)alkyl(C=O)(C1-C8)alkyl-, (C6-C10)aryl-, (C2-Cg) heteroaryl-, (C6-C10) aryloxy-, H2N(C=O)-, H2N (C=O)(Ci-C8)alkyl-, (C1-

C8) alkylNH(C=O)-, (C1-C8)alkyl-NH(C=O)(C1-C8)alkyl-, [(C1-C8)alkyl]2N(C=O)-, [(C1-C8) alkyl] 2N (C=O) (C1-C8) alkyl-, (C3-C8) cycloalkyl-, (C1-C8)alkylSO2-, NC(C1-C8)-alkyl(C=O)NH-, H2N(C=O)NH- or H2N(C=O)NH-(C1-C8)-alkyl-,

R5 is abound or a (C1-C8)-alkyl-,

R6 is independently hydroxy, amine or (C1-C8)-alkyl-NH, and

R7 is independently hydrogen, hydroxyl, (C1-C8)-alkyloxy or (C1-C8)-alkyl-

for the treatment and prevention of edometriosis

Particularly favourable embodiments of the present invention are the following compounds as reported in WO2004/055031

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzvl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzvl) phosphonic acid monoethyl ester,

5-Chloro-2-{2-[4-(4-fluoro-benzvl)-(2R5S)-2,5-dimethYl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonamidic acid

In another aspect, this invention provides pharmaceutical compositions useful in treating endometriosis in a human female in need of such treatment, which composition comprises a therapeutically effective amount of a compound of formula (Ia) as described above, and a pharmaceutically acceptabe excipient

In another aspect, this invention provides a method of treating and preventing endometriosis in a human female, which method comprises administering to a human female in need of such treatment a therapeutically effective amount of a compound of formula (Ia) as described above

In another aspect, this invention provides compounds of formula (Ia) for the preparation of a medicament for the treatment of endometriosis

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated

"Alkyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e g* , methyl, ethyl, *n*- propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), *n* -heptyl, and the like

"Alkylcarbonyl" refer to a radical of the formula -C(O)-R_a where R_a is an alkyl radical as defined above, *e g* , acetyl, ethylcarbonyl, *n*-propylcarbonyl, and the like

"Alkylcarbonylalkyl" refers to a radical of the formula - R_a-C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e.g* , (acetyl)methyl, 2-(acetyl)ethyl, 4- (ethylcarbonyl)butyl, and the like

"Alkylcarbonylamino" refers to a radical of the formula -N(H)-C(O)-R_a where R_a is an alkyl radical as defined above, *e g* , acetylamino, ethylcarbonylamino, n-propylcarbonylamino, and the like.

"(Alkylcarbonyl)(alkyl) amino" refers to a radical of the formula -N(R_a)-C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e g* , *N*-methyl-*N*-acetylamino, *N*-ethyl-*N*- (ethylcarbonyl)amino, and the like

"Alkylcarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, acetylammomethyl, 2- (acetylamino)ethyl, 4-(ethylcarbonylamino)butyl, and the like

"(Alkylcarbonyl)(alkyl)aminoalkyl" refers to a radical of the formula -R_a-N(R_a)-C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, (*N*-methyl-*N*-acetylamino)methyl, 2-(*N*-ethyl-*N*-(ethylcarbonyl)amino) propyl, and the like.

"Alkylthio" refers to a radical of the formula -S-R_a where R_a is an alkyl radical as defined above, *e.g* , methylthio, ethylthio, *n*- propylthio, and the like.

"Alkylsulfinyl" refers to a radical of the formula -S(O)R_a where R_a is an alkyl radical as defined above, *e g* , methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, and the like.

"Alkylsulfonyl" refers to a radical of the formula -S(O)$_2$$R_a$ where R_a is an alkyl radical as defined above, *e g* , methylsulfonyl, ethylsulfonyl, *n*- propylsulfonyl, and the like.

"Alkylthioalkyl" refers to a radical of the formula - R_a-S-R_a where each R_a is independently an alkyl radical as defined above, *e g* , methylthiomethyl, 2-methylthioethyl, 2-ethylthiopropyl, and the like.

"Alkylsulfinylalkyl" refers to a radical of the formula -R_a-S(O)-R_a where where each R_a is independently an alkyl radical as defined above, *e.g* , methylsulfinylmethyl, 2-methylsulfinylethyl, 2- ethylsulfinylpropyl, and the like

"Alkylsulfonylalkyl" refers to a radical of the formula $-R_a-S(O)_2-R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, methylsulfonylmethyl, 2-methylsulfonylethyl, 2-ethylsulfonylpropyl, and the like

"Alkylsulfonylamino" refers to a radical of the formula $-N(H)-S(O)_2-R_a$ where R_a is an alkyl radical as defined above, *e g.*, methylsulfonylamino, ethylsulfonylamino, *iso*-propylsulfonylamino, and the like

"Alkylsulfonylaminoalkyl" refers to a radical of the formula $-R_a-N(H)-S(O)_2-R_a$ where each R_a is independently an alkyl radical as defined above, *e g* , methylsulfonylaminomethyl, 2- (ethylsulfonylamino) ethyl, 3-(*iso*-propylsulfonylamino)propyl, and the like

"(Alkylsulfonyl)(alkyl)aminoalkyl" refers to a radical of the formula $-R_a-N(R_a)-S(O)_2-R_a$ where each R_a is independently an alkyl radical as defined above, *e g* , (methylsulfonyl)(methyl)aminomethyl, 2-((ethylsulfonyl)(methyl)amino) ethyl, 3-((*iso*-propylsulfonyl)(ethyl)amino)propyl, and the like.

"Alkenyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one double bond and having from two to eight carbon atoms, *e g* , ethenyl, prop-1-enyl, but-1-enyl, pent-1- enyl, penta-1,4-dienyl, and the like

"Alkenylcarbonylamino" refers to a radical of the formula $-N(H)-C(O)-R_c$ where R_c is an alkenyl radical as defined above, *e g.*, ethenylcarbonylamino, prop-2-enylcarbonylamino, but-2- enylcarbonylamino, and the like

"Alkynyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to eight carbon atoms, *e g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl, and the like

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above *e g* , methoxy, ethoxy, *n*-propoxy, 1-methylethoxy (*iso*-propoxy), *n*-butoxy, *n*-pentoxy 1,1- dimethylethoxy (*t*-butoxy), and the like

"Alkoxycarbonyl" refers to a radical of the formula $-C(O)OR_a$ where R_a is an alkyl radical as defined above, *e g* , methoxycarbonyl, ethoxycarbonyl, *n*- propoxycarbonyl, and the like

"Alkoxycarbonylalkyl" refers to a radical of the formula $-R_a-C(O)OR_a$ where each R_a is independently an alkyl radical as defined above, e.g., methoxycarbonylmethyl, 2-(ethoxycarbonyl)ethyl, 2- (methoxycarbonyl)propyl, and the like

"Alkoxyalkylcarbonyloxyalkyl" refers to a radical of the formula $-R_a-OC(O)-R_a-OR_a$ where each R_a is independently an alkyl radical as defined above, *e g* ,

methoxymethylcarbonyloxymethyl, 2-(2-(2- (ethoxy)ethylcarbonyloxy)ethyl) ethyl, 2-(3-(2-(ethoxy)ethylcarbonyloxy) propyl)ethyl, and the like

"Alkoxycarbonylamino" refers to a radical of the formula -N(H)-C(O)-OR_a where R_a is an alkyl radical as defined above, *e g* , methoxycarbonylamino, ethoxycarbonylamino, *iso*propoxycarbonylamino, and the like

"(Alkoxycarbonyl)(alkyl)amino" refers to a radical of the formula -N(R_a)(C(O)OR_a) where each R_a is independently an alkyl radical as defined above, *e.g* , *N*-methyl-*N*- methoxycarbonylamino, *N*-ethyl-*N*-ethoxycarbonylamino, and the like

"Alkoxycarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-OR_a where each R_a is independently an alkyl radical as defined above, *e g* , methoxycarbonylaminomethyl, 2-(ethoxycarbonylamino) ethyl, *iso*propoxycarbonylaminomethyl, and the like.

"(Alkoxycarbonyl)(alkyl)aminoalkyl" refers to a radical of the formula - R_a-N(R_a)(C(O)OR_a) where each R_a is independently an alkyl radical as defined above, *e g* , *N*-methyl-*N*-methoxycarbonylaminomethyl, 2-(*N*-ethyl- *N*-ethoxycarbonylamino)ethyl, and the like

"(Alkoxy)aralkyl" refers to an aralkyl radical wherein the alkyl group therein is substituted by an alkoxy radical as defined above, *e g* , 2-phenyl- 1-methoxyethyl, phenyl(methoxy)methyl, and the like

"Alkoxyalkylcarbonylamino" refers to a radical of the formula -N(H)-C(O)- R_a-O-R_a where each R_a is an alkyl radical as defined above, e.g., methoxymethylcarbonylamino, ethoxyethylcarbonylamino, methoxyethylcarbonylamino, and the like

"Alkoxycarbonylalkylcarbonylamino" refers to a radical of the formula - N(H)-C(O)-R_a-C(O)OR_a where each R_a is independently an alkyl radical as defined above, *e.g.* ethoxycarbonylmethylcarbonylamino, methoxycarbonylmethylcarbonylamino, (2-ethoxycarbonylethyl)carbonylamino, (2-methoxycarbonylethyl)carbonylamino, and the like

"Alkoxycarbonylalkylcarbonylaminoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-R_a-C(O) OR_a where each R_a is independently an alkyl radical as defined above, *e g* , ethoxycarbonylmethylcarbonylaminomethyl, 2-(methoxycarbonylmethylcarbonylamino)ethyl, 1-((2-ethoxycarbonylethyl) carbonylamino)ethyl, (2-methoxycarbonylethyl)carbonylaminomethyl, and the like

"(Alkoxycarbonylalkyl)aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a-C(O)-OR_a where each R_a is independently an alkyl radical as defined above, *e.g* , (methoxycarbonylmethyl) aminocarbonyl, (2-

(ethoxycarbonyl)ethyl)aminocarbonyl, (1- (methoxycarbonyl)ethyl)aminocarbonyl, and the like

"(Alkoxycarbonylalkyl)ureidoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-N(H)-R_a-C(O)-OR_a where each R_a is independently an alkyl radical as defined above and where the nitrogen to which -R_a- C(O)-OR_a is attached is indicated as "*N*", *e g* , (ethoxycarbonylmethyl)ureidomethyl, (2-(ethoxycarbonyl)ethyl)ureidomethyl, 2-((2-(ethoxycarbonylmethyl) ureidomethyl, and the like

"(Alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(R_a)-C(O)-R_a- C(O)-OR_a where each R_a is independently an alkyl radical as defined above, *e g.*, (methoxycarbonylmethylcarbonyl)(methyl) glycinamido, ((2-ethoxycarbonylethyl)carbonyl)(ethyl)glycinamido, and the like

"(Alkoxyalkylcarbonyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H)-C(O)-R_a-O-R_a where each R_a is independently an alkyl radical as defined above, *e g.*, (methoxyacetyl)glycinamido, (ethoxyacetyl)glycinamido, and the like.

"Alkylene chain" refers to straight or branched chain divalent radical consisting solely of carbonyl and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e g* , methylene, ethylene, propylene, *n*-butylene, and the like

"Alkylidene chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from one to eight carbon atoms, wherein the unsaturation is present only as double bonds and wherein a double bond can exist between the first carbon of the chain and the rest of the molecule, *e g* , ethylidene, propylidene, *n*-butylidene, and the like

"Amino" refers to the radical -NH_2

"Aminoalkyl" refers to a radical of the formula -$R_a NH_2$ where R_a is an alkyl radical as defined above, *e. g* , aminomethyl, 2-aminoethyl, 3-aminopropyl, 2-aminopropyl, and the like

"Aminoalkylamino" refers to a radical of the formula -N(H)- R_a-NH_2 where R_a is an alkyl radical as defined above, *e g.*, aminomethylamino, (2-aminoethyl)amino, (2-aminopropyl)amino, and the like

"Aminoalkoxy" refers to a radical of a formula -OR_a- NH_2 where R_a is an alkyl radical as defined above, *e g* , aminomethoxy, 2- aminoethoxy, 3-aminopropoxy, 2-aminopropoxy, 4-aminobutoxy, and the like

"Aminocarbonyl" refers to the radical -C(O)NH_2

"Aminocarbonylglycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H)-C(O)-NH_2

"(Aminocarbonyl)(alkyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(R_a)-C(O)-NH_2 where R_a is an alkyl radical as defined above and where the nitrogen with the R_a substituent is designated as "*N*", *e.g*, (aminocarbonyl)(*N'*-methyl)glycinamido, (aminocarbonyl)(*N'*- ethyl)glycinamido, and the like.

"Aminocarbonylalkyl" refers to a radical of the formula - R_a-C(O)NH_2 where R_a is an alkyl radical as defined above, *e g*, aminocarbonylmethyl, 2-(aminocarbonyl)ethyl, 2-(aminocarbonyl)propyl, and the like

"(Aminocarbonylalkyl)aminocarbonyl" refers to a radical of the formula - C(O)-N(H)-R_a-C(O)-NH_2 where R_a is an alkyl radical as defined above, *e g*, (aminocarbonylmethyl)aminocarbonyl, (2-aminocarbonylethyl)aminocarbonyl, (1-aminocarbonylethyl)aminocarbonyl, and the like

"(Aminoalkyl) aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a -NH_2 where R_a is an alkyl radical as defined above, *e g*, (aminomethyl) aminocarbonyl, (2-aminoethyl)aminocarbonyl, (1-aminoethyl)aminocarbonyl, and the like.

"Amidino" refers to the radical -C(NH)NH_2.

"Aryl" refers to a phenyl or naphthyl radical. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents selected from the group consisting of hydroxy, mercapto, halo, alkyl, alkenyl, alkynyl, phenyl, phenylalkyl, phenylalkenyl, alkoxy, phenoxy, phenylalkoxy, haloalkyl, haloalkoxy, formyl, nitro, cyano, amidino, cycloalkyl, hydroxyalkyl, alkoxyalkyl, phenoxyalkyl, phenylalkoxyalkyl, amino, monoalkylamino, dialkylamino, monophenylamino, monophenylalkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monophenylaminoalkyl, monophenylalkylaminoalkyl, alkylcarbonyl, carboxy, alkoxycarbonyl, carpoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, as defined herein

"Arylcarbonyl" refers to a radical of the formula -C(O)R_b where R_b is an aryl radical as defined above, *e g*, phenylcarbonyl and naphthalen-2-ylcarbonyl, and the like

"Arylcarbonylalkyl" refers to a radical of the formula -R_aC(O)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, phenylcarbonylmethyl, 2-(phenylcarbonyl)ethyl, 3-(naphthalen-2-ylcarbonyl) propyl, and the like

"Arylcarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e g*

, (4-methoxyphenyl)carbonylaminomethyl, 2-((4-fluorophenyl)carbonylamino) ethyl, 1-((4-chlorophenyl)carbonylamino)ethyl, and the like.

"Arylsuffonyl" refers to a radical of the formula $-S(O)_2-R_b$ where R_b is an aryl radical as defined above, *e g* , phenylsulfonyl, (4- chlorophenyl)sulfonyl, (3-nitrophenyl)sulfonyl, and the like

"Arylsulfonylamino" refers to a radical of the formula $-N(H)-S(O)_2-R_b$ where R_b is an aryl radical as defined above, *e g* , phenylsulfonylamino, (4-chlorophenyl)sulfonylamino, (4-fluorophenyl)sulfonylamino, (3-nitrophenyl) sulfonylamino), and the like

"Arylsulfonylaminoalkyl" refers to a radical of the formula $-R_a-N(H)-S(O)_2-R_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e g* , phenylsulfonylaminomethyl, (4-chlorophenyl) sulfonylaminomethyl, 2-((4-fluorophenyl)sulfonylamino)ethyl, 1-((3- nitropnenyl)sulfonylamino)ethyl, and the like.

"(Arylsulfonyl) (alkyl)aminoalkyl" refers to a radical of the formula $-R_a-N(R_a)-S(O)_2-R_b$ where each R_a is independently an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g* , (phenylsulfonyl)(methyl) aminomethyl, ((4-chlorophenyl)sulfonyl)(ethyl)aminomethyl, 2-(((4-fluorophenyl)sulfonyl)(methyl)amino)ethyl, 1-(((3-nitrophenyl)sulfonyl) (ethyl)amino)ethyl, and the like.

"(Alkoxycarbonylaminoalkylcarbonyl)glycinamido" refers to a radical of the formula $-N(H)-C(O)-CH_2-N(H)-C(O)-N(H)-C(O)-OR_a$ where R_a is an alkyl radical as defined above, *e.g* , (ethoxycarbonylaminocarbonyl)glycinamido, (methoxycarbonylaminocarbonyl)glycinamido, and the like.

"Arylcarbonylglycinamido" refers to a radical of the formula $-N(H)-C(O)-CH_2-N(H)-C(O)-R_b$ where R_b is an aryl radical as defined above, e g , phenylcarbonylglycinamido, (4-fluoro-3-trifluoromethylphenyl) carbonylglycinamido, (4-fluorophenyl)carbonylglycinamido, and the like

"(Arylcarbonyl)(alkyl)glycinamido" refers to a radical of the formula $-N(H)-C(O)-CH_2-N(R_a)-C(O)-R_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above and the nitrogen to which the R_a radical is attached is designated as "*N*", *e g* , (phenylcarbonyl)(*N'*-methyl) glycinamido, ((4-fluoro-3-trifluoromethylphenyl)carbonyl) (*N'*-ethyl)glycinamido, ((4-fluorophenyl)carbonyl)(*N'*-methyl) glycinamido, and the like

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, benzyl, and the like

"Aralkylcarbonyl" refers to a radical of the formula -C(O)-R_d where R_d is an aralkyl radical as defined above, *e g* , benzylcarbonyl, 1-(phenyl)ethylcarbonyl, and the like

"Aralkylcarbonylalkyl" refers to a radical of the formula -R_aC(O)R_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e g.*, benzylcarbonylmethyl, 2-(1-(phenyl)ethylcarbonyl)ethyl, and the like

"Aralkenyl" refers to a radical of the formula -$R_c$$R_b$ where R_b is an aryl radical as defined above and R_c is an alkenyl radical as defined above, *e.g.*, 3-phenylpropylid-1-enyl, and the like

"Aryloxy" refers to a radical of the formula -OR_b where R_b is an aryl radical as defined above, *e g* , phenoxy and naphthoxy, and the like.

"Aralkoxycarbonyl" refers to a radical of the formula -C(O)OR_d where R_d is an aralkyl radical as defined above, *e.g* , benzyloxycarbonyl, and the like.

"Aralkoxycarbonylalkyl" refers to a radical of the formula -R_a C(O)OR_d where R_a is an alkyl radical as defined above and R_a is an aralkyl radical as defined above, *e g* , benzyloxycarbonylmethyl, 2- (benzyloxycarbonyl)ethyl, 3-((naphthalen-2-yl)oxy)carbonyl)propyl, and the like

"Aryloxyalkyl" refers to a radical of the formula - R_a-OR_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above. *e.g.*, phenoxymethyl, 2-(phenoxy) ethyl, 3-(phenoxy)propyl, and the like

"Aryloxyalkylcarbonyloxyalkyl" refers to a radical of the formula -R_a-OC(O)-R_a- OR_b where each R_a is independently an alkyl radical as defined above and R_b is an aryl radical as defined above, *e g* , phenoxymethylcarbonyloxymethyl, (2-phenoxyethyl)carbonyloxymethyl, 3-((2-phenoxyethyl)carbonyloxy)propyl, and the like

"Aralkoxy" refers to a radical of the formula - OR_d where R_d is an aralkyl radical as defined above, *e g* , benzyloxy, and the like

"Aralkoxylalkyl" refers to a radical of the formula -R_a-OR_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e g.*, benzyloxymethyl, 2- phenylethoxymethyl, and the like ,

"Aralkoxyalkylcarbonyloxyalkyl" refers to a radical of the formula -R_a-OC(O)-R_a-OR_d where each R_a is independently an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e.g.*, benzyloxymethylcarbonyloxymethyl, (2-(phenyl) ethoxymethyl)carbonyloxymethyl, 2-((2-(phenyl)ethoxymethyl)carbonyloxy) ethyl, and the like

"Alkoxyalkyl" refers to a radical of the formula $-R_a OR_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, methoxyethyl, ethoxymethyl, propoxymethyl, propoxyethyl, and the like

"Alaninamido" refers to a radical of the formula $-N(H)- C(O)-C(CH_3)H-NH_2$.

"Alaninamidoalkyl" refers to a radical of the formula $-R_a-N(H)-C(O)-C(CH_3)H-NH_2$ where R_a is an alkyl radical as defined above, *e g* , alaninamidomethyl, 2-(alaninamido)ethyl, 1-(alaninamido)ethyl, 3- (alaninamido)propyl, and the like.

"Azidoalkyl" refers to radical of the formula $-R_a-N_3$ where R_a is an alkyl radical as defined above, *e.g* , 2-azidoethyl, 3-azidopropyl, 2-azidopropyl, 4-azidobutyl, and the like

"Benzyl" refers to a radical of the formula $-CH_2-R_h$ where R_h is a phenyl radical optionally substituted by one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, alkenyl, nitro, cyano, amino, monoalkylamino, dialkylamino, alkylcarbonyl, carboxy, alkoxycarbonyl, and aminocarbonyl.

"Benzylcarbonyl" refers to a radical of the formula $-C(O)-CH_2- R_h$ where R_h is a phenyl radical as defined above, *e g* , (4-methoxybenzyl)carbonyl, (3-fluorobenzyl)carbonyl, and the like

"Carboxy" refers to the radical -C(O)OH.

"Carboxyalkyl" refers to the radical of the formula $-R_a-C(O)OH$ where R_a is an alkyl radical as defined above, *e g* , carboxymethyl, 2- carboxyethyl, 3-carboxypropyl, and the like.

"(Carboxyalkyl) aminocarbonyl" refers to a radical of the formula $-C(O)-N(H)-R_a-C(O)OH$ where R_a is an alkyl radical as defined above, *e.g* , (carboxymethyl)aminocarbonyl, (2- carboxyethyl)aminocarbonyl, (1-carboxyethyl)aminocarbonyl, and the like

"Carbocyclic ring system" refers to a stable 3- to 15-membered ring radical consisting solely of carbon and hydrogen atoms For purposes of this invention, the carbocyclic ring system radical may be a monocyclic, bicyclic or tricyclic ring system, and may include fused or bridged ring systems, and the ring system may be partially or fully saturated or aromatic, and the carbon atoms in the ring system may be optionally oxidized Examples of such carbocyclic ring system radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclohexyl, norbornane, norbornene, adamantyl, bicyclo[2.2.2]octane, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, and the like

"Cycloalkyl" refers to a stable 3- to 10-membered monocyclic or bicyclic radical which is saturated, and which consist solely of carbon and hydrogen atoms, *e g*, cyclopropyl, cyclobutyl, cyclobutyl, cyclohexyl, decalinyl and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, halo, hydroxy, amino, nitro, alkoxy, carboxy, phenyl and alkoxycarbonyl.

"Cycloalkylalkyl" refers to a radical of the formula $-R_a-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e g*, cyclopropylmethyl, 2- cyclobutylethyl, 3-cyclohexylpropyl, and the like

"Cycloalkylamino" refers to a radical of the formula $-N(H)-R_e$ where R_e is a cycloalkyl radical as defined above, *e g*, cyclopropylamino, cyclobutylamino, cyclohexylamino, and the like

"Cycloalkylaminoalkyl" refers to a radical of the formula $-R_a-N(H)-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e g*, cyclopropylaminomethyl, 2-(cyclobutylamino)ethyl, cyclohexylaminomethyl, and the like

"(Cycloalkylalkyl)amino" refers to a radical of the formula $-N(H)-R_a-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e g*, (cyclopropylmethyl)amino, (2-cyclobutylethyl) amino, (3-cyclohexylpropyl)amino, and the like

"(Cycloalkylalkyl)aminoalkyl" refers to a radical of the formula $-R_a-N(H)-R_a-R_e$ where each R_a is independently an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e g*, (cyclopropylmethyl)aminomethyl, 2-((2-cyclobutylethyl)amino)ethyl, (3-cyclohexylpropyl)aminomethyl, and the like

"Cycloalkylcarbonylamino" refers to a radical of the formula $-C(O)-N(H)-R_e$ where R_e is a cycloalkyl radical as defined above, *e g.*, cyclopropylcarbonylamino, (2-phenylcyclopropyl)carbonylamino, cyclohexylcarbonylamino, 4-cyanodecalinylcarbonylamino cyclopentylcarbonylamino, and the like

"Cycloalkylcarbonylaminoalkyl" refers to a radical of the formula $-R_a-C(O)-N(H)-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e g*, cyclopropylcarbonylaminomethyl, 2-((2- phenylcyclopropyl) carbonylamino)ethyl, 1-(cyclohexylcarbonylamino)ethyl, (3-phenylcyclopentyl)carbonylaminomethyl, and the like

"Cycloalkylalkylcarbonylamino" refers to a radical of the formula $-C(O)- N(H)-R_a-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as

defined above, *e.g.*, (cyclopropylmethyl) carbonylamino, ((2-phenylcyclopropyl)methyl)carbonylamino, (2- cyclohexylethyl)carbonylamino, (1-cyclohexylethyl)carbonylamino, and the like

"Cyano" refers to the radical -CN.

"Cyanoalkyl" refers to a radical of the formula -R_aCN where R_a is an alkyl radical as defined above, cyanomethyl, 2- (cyano)ethyl, 3-(cyano)propyl, and the like

"DMF" refers to N,N- dimethylformamide

"DMSO" refers to dimethylsulfoxide.

"Dialkylamino" refers to a radical of the formula -N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylamino, methylethylamino, diethylamino, dipropylamino, ethylpropylamino, and the like.

"Dialkylaminoalkyl" refers to a radical of the formula -R_a-N(R_a) R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminomethyl, methyethylaminomethyl, 2-diethylaminoethyl, 3-dipropylaminopropyl, and the like

"Dialkylaminocarbonyl" refers to a radical of the formula -C(O)N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e g* , dimethylaminocarbonyl, methylethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, ethylpropylaminocarbonyl, and the like

"Dialkylaminocarbonylalkyl" refers to a radical of the formula -R_a-C(O)N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e g.*, dimethylaminocarbonylmethyl, 2-(methylethylaminocarbonyl)ethyl, 3-(diethylaminocarbonyl)propyl, 2- (dipropylaminocarbonyl)propyl, and the like

"Dialkylaminocarbonyloxyalkyl" refers to a radical of the formula -R_a-O-C(O)-N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e g*, dimethylaminocarbonyloxymethyl, 2- (methylethylaminocarbonyloxy)ethyl, 3-(diethylaminocarbonyloxy)propyl, 2- (dipropylaminocarbonyloxy)propyl, and the like

"Dialkylureido" refers to a radical of the formula -N(H)- C(O)- N(R_a)(R_a) or a radical of the formula -N(R_a)-C(O)-N(R_a)H where each R_a is independently an alkyl radical as defined above and the attaching nitrogen is designated as "N" and the other nitrogen is designated as "N", *e g* , *N'*,*N'*-di(methyl) ureido, *N'*-methyl-*N'*-ethylureido, *N'*,*N'*-di(ethyl) ureido, *N'*,*N'*-di(propyl)ureido, *N*-methyl-*N'*- ethylureido, and the like

"Diarylureido" refers to a radical of the formula -N(H)-C(O)-N(R_b)(R_b) or a radical of the formula -N(R_b)-C(O)-N(R_b)H where each R_b is independently an aryl radical as defined above and the attaching nitrogen is designated as "*N*" and the other

nitrogen is designated as "*N'*, *e g* , *N',N'*-di(phenyl)ureido, *N'*-phenyl-*N'*-(3-nitro) phenylureido, *N',N'*-di(4-methoxyphenyl)ureido, *N',N'*-di(4- chlorophenyl) ureido, *N*-4-chlorophenyl-*N'*-(3-chlorophenyl) ureido and the like

"Dialkylureidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-N(R_a) (R_a) or a radical of the formula -R_a-N(R_a)-C(O)-N(R_a)H where each R_a is independently an alkyl radical as defined above and the attached nitrogen is designated as "*N*" and the other nitrogen is designated as "*N'*", *e g* , *N',N'*- di(methyl) ureidomethyl, 2-(*N'*-methyl-*N'*-ethylureido)ethyl, 1-(*N',N'*-di(ethyl)ureido)ethyl, 3-(*N',N'*-di(propyl)ureido)propyl, 2-(*N*-methyl-*N'*-ethylureido)ethyl, and the like

"Formyl" refers to the radical -C(O)H.

"Formylalkyl" refers to a radical -R_a-C(O)H where R_a is an alkyl radical as defined above, *e.g* , formylmethyl, 2-(formyl)ethyl, 3-(formyl)propyl, and the like

"Glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2 -NH_2

"Glycinamidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)- CH_2- NH_2 where R_a is an alkyl radical as defined above, *e.g.*, glycinamidomethyl. 2-(glycinamido)ethyl, 1-(glycinamido)ethyl, 3- (glycinamido)propyl, and the like

"Guanidino" refers to the radical -N(H)-C(NH)-NH_2

"Halo" refers to bromo, chloro, iodo or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo- 2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like

"Haloalkoxy" refers to a radical of the formula -OR_f where R_f is an haloalkyl radical as defined above, *e g* , trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3- bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like

"Haloalkylcarbonylamino" refers to a radical of the formula -N(H)-C(O) -R_f where R_f is an haloalkyl radical as defined above, *e g* , trifluoromethylcarbonylamino, trifluoromethylcarbonylamino, 2-bromoethylcarbonylamino, and the like.

"(Haloalkylcarbonyl)ureido" refers to a radical of the formula - N(H)-C(O)-N(H)-C(O)-R_f where R_f is a haloalkyl radical as defined above, *e g* , (trichloromethylcarbonyl)ureido, (3-fluoropropylcarbonyl)ureido, and the like

"(Haloalkyl)(alkyl)ureidoalkyl" refers to a radical of the formula -R_a-N(R_a)-C(O)-N(H)-R_f or a a radical of the formula -R_a- N(R_f)-C(O)-N(H)-R_a or a radical of the formula -R_a-N(H)-C(O)-N(R_a) R_f where each R_a is independently an alkyl radical as defined above and R_f is an haloalkyl radical as defined above and terminal nitrogen is

designated as "*N*" and the other nitrogen is designated as "*N'*", *e.g*, *N'*-(2-chloroethyl)-*N*-(methyl)ureidomethyl, and 2-(*N'*-(2- chloroethyl)-*N*-(methyl)ureido)ethyl, and the like.

"Haloalkylcarbonylaminoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-R_f where R_a is an alkyl radical as defined above and R_f is an haloalkyl radical as defined above, *e g*, trifluoromethylcarbonylaminomethyl, 2-(trifluoromethylcarbonylamino)ethyl, and the like.

"Hydroxy" refers to the radical -OH

"Hydroxyalkyl" refers to a alkyl radical as defined above that is substituted by a hydroxy radical, *e g*, hydroxymethyl, 2- hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 4-hydroxybutyl, 3- hydroxybutyl, and the like

"(Hydroxyalkyl)aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a-OH where R_a is an alkyl radical as defined above, *e g*, hydroxymethylaminocarbonyl, (2-hydroxyethyl)aminocarbonyl, (1- hydroxyethyl)aminocarbonyl, and the like

"Hydroxyalkoxy" refers to a radical of the formula -OR_a-OH where R_a is an alkyl radical as defined above, *e g*, 2- hydroxyethoxy, 2-hydroxypropoxy, 4-hydroxybutoxy, 3-hydroxybutoxy, and the like

"(Hydroxyalkoxy)carbonyl" refers to a radical of the formula - C(O)-OR_a-OH where R_a is an alkyl radical as defined above, *e g*, (2-hydroxyethoxy)carbonyl, (2-hydroxypropoxy)carbonyl, (4-hydroxybutoxy)carbonyl, (3-hydroxybutoxy) carbonyl, and the like

"(Hydroxy)aralkyl" refers to an aralkyl radical as defined above wherein the alkyl radical therein is substituted by a hydroxy radical, *e g*, (phenyl)(hydroxy)methyl, 2-phenyl-1- hydroxyethyl, 2-phenyl-3-hydroxypropyl, and the like

"(Hydroxyalkylthio) alkyl" refers to an alkylthioalkyl radical as defined above that is substituted by an hydroxy radical, *e g*, 2- hydroxyethylthiomethyl, 2-(hydroxymethylthio)ethyl, and the like

"Hydroxyalkenyl" refers to an alkenyl radical as defined above that is substituted by a hydroxy radical, *e g*, 3-hydroxyprop-1-enyl, 4- hydroxybut-1-enyl, 4-hydroxypent-1- enyl, 5-hydroxypenta-1,3-dienyl, and the like

"Hydroxyalkynyl" refers to an alkynyl radical as defined above that is substituted by a hydroxy radical, e.g, 3- hydroxyprop-ynyl, 4-hydroxypent-2-ynyl, 1-hydroxybut-3-ynyl, and the like

"(Hydroxy)cycloalkylalkyl" refers to a radical of the formula - R_a(OH)-R_e where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above and

where the OH radical is a substituent on any carbon of the R_8 radical, *e g*, 2-cyclopropyl-1-hydroxyethyl, (4-hydroxycyclohexyl)methyl, and the like.

"Hydroxyalkylaminoalkyl" refers to a monoalkylaminoalkyl radical as defined below that is substituted by a hydroxy radical, *e g*., 2-hydroxyethylaminomethyl, 2-(3-hydroxypropylamino)ethyl, and the like

"Hydroxyamidino" refers to a radical of the formula - $C(NH_2)=NOH$.

"Heterocyclic ring system" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclic ring system radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems, and the nitrogen, carbon or sulfur atoms in the heterocyclic ring system radical may be optionally oxidized, the nitrogen atom may be optionally quaternized; and the heterocyclic ring system may be partially or fully saturated or aromatic. The heterocyclic ring system may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic radicals include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furanyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, triazinyl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone

"Heterocyclyl" refers to a heterocyclic ring system as defined above Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include a heterocyclic ring system as defined above which is optionally substituted by one or more substituents selected from the group consisting of hydroxy, mercapto, halo, alkyl, alkenyl, alkynyl, phenyl, phenylalkyl, phenylalkenyl, alkoxy, phenoxy, phenylalkoxy, haloalkyl, haloalkoxy, formyl, nitro,

cyano, amidino, cycloalkyl, hydroxyalkyl, alkoxyalkyl, phenoxyalkyl, phenylalkoxyalkyl, amino, monoalkylamino, dialkylamino, monophenylamino, monophenylalkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monophenylaminoalkyl, monophenylalkylaminoalkyl, carboxy, alkoxycarbonyl, phenylcarbonyl, benzylcarbonyl, alkylcarbonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, phenylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, ureido, monoalkylureido, monophenylureido, monobenzylureido, as defined herein

"Heterocyclylalkyl" refers to a radical of the formula $-R_aR_g$ where R_a is an alkyl radical as defined above and R_g is a heterocyclyl radical as defined above, *e g* , indolinylmethyl or imidazolylmethyl, and the like

"Heterocyclylamino" refers to a radical of the formula - N(H)- R_g where R_g is a heterocyclyl radical as defined above, *e g* , oxazol-2-ylamino; piperidin-4- ylamino, and the like

"Heterocyclylaminoalkyl" refers to a radical of the formula $-R_a$-N(H)-R_g where R_a is an alkyl radical as defined above and R_g is a heterocyclyl radical as defined above, *e g* , oxazol-2-ylaminomethyl, 2-(oxazol-2-ylamino)ethyl, piperidin-4-ylaminomethyl, 2-(piperidin-4-ylamino)ethyl, and the like

"Heterocyclylcarbonylamino" refers to a radical of the formula -N(H)-C(O)- R_g where R_g is a heterocyclyl radical as defined above, *e g.*, piperidin-4-ylcarbonylamino, furan- 2-ylcarbonylamino, morpholin-4-ylcarbonylamino, and the like

"Heterocyclylcarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-R_g where R_a is an alkyl radical as defined above and R_g is a heterocyclyl radical as defined above, *e.g., piperidin-4- ylcarbonylaminomethyl, 2-(furan-2-*ylcarbonylamino)ethyl, 1-(morpholin-4- ylcarbonylamino)ethyl, and the like

"Mercapto" refers to the radical -SH

"Mercaptoalkyl" refers to a radical of the formula - R_a-SH where R_a is an alkyl radical as defined above, *e g* , mercaptomethyl, 2-mercaptoethyl, 3- mercaptopropyl, 2-mercaptobutyl and the like

"Monoalkylamino" refers to a radical of the formula -N(H)R_a where R_a is an alkyl radical as defined above, *e.g* , methylamino, ethylamino, propylamino, and the like.

"Monoalkylaminoalkyl" refers to a radical of the formula $-R_a$-N(H)R_a where each R_a is independently an alkyl radical as defined above, *e g* , methylaminomethyl, ethylaminomethyl, 2-(propylamino)ethyl, and the like.

"(Monoalkylamino)aralkyl" refers to a radical of the formula - R_d-N(H)R_a where R_a is an alkyl radical a defined above and R_d is an aralkyl radical as defined above, *e.g*, (methylamino) (phenyl) methyl, 1-(ethylamino)-1-(4-methoxyphenyl)ethyl, 2-(isopropylamino)-3-(3-chlorophenyl)propyl, and the like

"Monoarylamino" refers to a radical of the formula -N(H)R_b where R_b is an aryl radical as defined above, *e g*, phenylamino, (4-methoxyphenyl)amino, (3,4,5-trimethoxyphenyl) amino and the like

"Monoarylaminoalkyl" refers to a radical fo the formula - R_a-N(H)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e g*, phenylaminomethyl, 2-((4- methoxyphenyl)amino)ethyl, 3-((3,4,5-trimethoxyphenyl)amino)propyl, and the like

"Monoaralkylamino" refers to a radical of the formula - N(H)R_d where R_d is an aralkyl radical as defined above, *e g*, benzylamino, (3,4,5- trimethoxybenzyl)amino, (4-chlorobenzyl)amino,and the like

"Monoaralkylaminoalkyl" refers to a radical of the formula -R_a-N(H)R_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e g*, benzylaminomethyl, (3- phenylpropyl)aminomethyl, 2-(benzylamino)ethyl, and the like

"Monoalkylaminocarbonyl" refers to a radical of the formula -C(O)N(H)R_a where R_a is an alkyl radical as defined above, *e g.*, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, and the like.

"Monoalkylaminocarbonylalkyl" refers to a radical of the formula -R_a-C(O)N(H)R_a where each R_a is independently an alkyl radical as defined above, *e g.*, methylaminocarbonylmethyl, 2- (ethylaminocarbonyl)ethyl, 3-(propylaminocarbonyl)propyl, and the like.

"Monoarylaminocarbonyl" refers to a radical of the formula -C(O) N(H)R_b where R_b is an aryl radical as defined above, *e g*, phenylaminocarbonyl,(3,4,5-*trs*(trifluoromethoxy)phenyl)-aminocarbonyl, (4-chlorophenyl) aminocarbonyl, and the like

"Monoarylaminocarbonylalkyl" refers to a radical of the formula -R_a-C(O)N(H)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e g*, phenylaminocarbonylmethyl, 2-((4-chlorophenyl) aminocarbonyl)ethyl, 3-((3,4,5-trimethoxyphenyl)aminocarbonyl)propyl, and the like

"Monoaralkylaminocarbonyl" refers to a radical of the formula -C(O)N(H)R_d where R_d is an aralkyl radical as defined above, *e g.*, benzylaminocarbonyl, (3, 4,5-

tris(trifluoromethoxy)benzyl)-aminocarbonyl, (4-chlorobenzyl) aminocarbonyl, and the like

"Monoaralkylaminocarbonylalkyl" refers to a radical of the formula -R_a-C(O)N(H)R_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e.g.*, benzylaminocarbonylmethyl, 2-((4-chlorobenzyl) aminocarbonyl)ethyl, 3-((3,4,5-trimethoxybenzyl)aminocarbonyl)propyl, and the like

"(Monoalkylaminocarbonylalkyl)aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a-C(O)-N(H)R_a where each R_a is independently an alkyl radical as defined above, *e g.*, (methylaminocarbonylmethyl)aminocarbonyl, (2-(methylaminocarbonyl)ethyl)aminocarbonyl, (1-(ethylaminocarbonyl)ethyl) aminocarbonyl, and the like

"Monoalkylalaninamido" refers to radical of the formula -N(H)-C(O)-C(CH_3)H-N(H)R_a where R_a is an alkyl radical as defined above and the attached nitrogen is designated as "*N*" and the other nitrogen (having the R_a substituent) is designated as "*N'*", *e.g* , *N'*-methylalanimido, *N'*-ethylalanimido, and the like

"Monoalkylglycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H) R_a where R_a is an alkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen (having the R_a substituent) is designated as "*N'*", *e g* , *N'*-methylglycinamido. *N'*-ethylglycinamido, and the like.

"(Monoarylaminocarbonyl) glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2- N(H)-C(O)-N(H)R_b where R_b is an aryl radical as defined above, *e.g* , ((4-phenoxyphenyl)aminocarbonyl)glycinamido, ((4-chlorophenyl)aminocarbonyl) glycinamido, (phenylaminocarbonyl)glycinamido, and the like

"(Monoarylaminocarbonyl)(alkyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(R_a)-C(O)- N(H)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above and the nitrogen to which R_a is attached is designated as "*N'*", *e g* , ((4-phenoxyphenyl) aminocarbonyl)(*N'*-methyl)glycinamido, ((4-chlorophenyl) aminocarbonyl)(*N'*-ethyl)glycinamido, (phenylaminocarbonyl)(*N'*-methyl)glycinamido, and the like

"(Monoaralkylaminocarbonyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H)-C(O)-N(H)R_d where R_d is an aralkyl radical as defined above, *e g* , ((4-phenoxybenzyl)aminocarbonyl)glycinamido, ((4-chlorobenzyl)aminocarbonyl)glycinamido, (benzylaminocarbonyl)glycinamido, and the like.

"(Monoaralkylaminocarbonyl)(alkyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2- N(R_a)-C(O)- N(H)R_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above and the nitrogen to which the R_a is attached is designated as "*N* ", *e g* , ((4-phenoxybenzyl)aminocarbonyl)(*N'*-methyl) glycinamido, ((4-chlorobenzyl)aminocarbonyl)(*N'*-ethyl)glycinamido, (benzylaminocarbonyl)(*N'*-methyl)glycinamido, and the like.

"Monoalkylureido" refers to a radical of the formula -N(H)-C(O)-N(H) R_a or a radical of the formula -N(R_a)-C(O)-NH_2 where R_a is an alkyl radical as defined above and the attaching nitrogen is designated as " *N'* and the other nitrogen is designated as "*N'*, *e. g* , *N'*-methylureido, *N'*-ethylureido, *N'*- propylureido, *N*-methylureido, *N*-ethylureido, *N*- propylureido, and the like.

"Monophenylureido" refers to a radical of the formula -N(H)-C(O)-N(H)R_h where R_h is a phenyl radical as defined above, and the attaching nitrogen is designated as "*N'*" and the other nitrogen is designated as "*N'*, *e g* , *N'*-phenylureido, *N'*-(4-nitrophenyl)ureido, *N'*-(3-chlorophenyl)ureido, and the like

"Monobenzylureido" refers to a radical of the formula -N(H)-C(O)-N(H)- CH_2-R_h where R_h is a phenyl radical as defined above, and the attaching nitrogen is designated as "*N'*" and the other nitrogen is designated as " *N'*", *e g.*, *N'*-benzylureido, *N'*-(4-nitrobenzyl) ureido, *N'*-(3-chlorobenzyl)ureido, and the like

"Monohaloalkylureido" refers to a radical of the formula -N(H)-C(O)-N(H) R_f or a radical of the formula -N(R_f)-C(O)-NH_2 where R_f is a haloalkyl radical as defined above and the attaching nitrogen is designated as "*N'*" and the other nitrogen is designated as "*N* ", *e g* , *N'*-chloromethylureido, *N'*-(2,2- difluoroethyl)ureido, *N'*-(3-chloropropyl)ureido, *N*- (trifluoromethyl)ureido, *N*-(pentafluoroethyl)ureido, *N*-(3- iodopropyl)ureido, and the like.

"Monoarylureido" refers to a radical of the formula -N(H)-C(O)-N(H)R_b or a radical of the formula -N(R_b) -C(O)-NH_2 where R_b is an aryl radical as defined above and the attaching nitrogen is designated as "*N'*" and the other nitrogen is designated as "*N'*", *e g* , *N'*-phenylureido, *N'*- (4-methoxyphenyl)ureido, *N'*-(3-chlorophenyl)ureido, *N*- phenylureido, *N*-(2-trifluoromethylphenyl)ureido, *N*-(4-chlorophenyl) ureido, and the like.

"Monoaralkylureido" refers to a radical of the formula -N(H)-C(O)-N(H)R_d or a radical of the formula -N(R_d) -C(O)-NH_2 where R_d is an aralkyl radical as defined above and the attaching nitrogen is designated as "*N'*" and the other nitrogen is designated as "*N'*", *e g* , *N'*- benzylureido, *N'*-(4-methoxybenzyl) ureido, *N'*-(3-

chlorobenzyl)ureido, *N*-benzylureido, *N*-(2- trifluoromethylbenzyl)ureido, *N*-(4-chlorobenzyl)ureido, and the like.

"(Monoalkyl)(monoaryl)ureido" refers to a radical of the formula -N(R_a)-C(O)-N(R_b)H, or a radical of the formula -N(R_b)-C(O)-N(R_a)H, or a radical of the formula -N(H)-C(O)-N(R_a)(R_b) where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, and where the attaching nitrogen is designated as "*N* " and the other nitrogen is designated as "*N'*", e g , *N*-methyl- *N'*-phenylureido, *N*-phenyl-*N'*-ethylureido, *N*- methyl-*N'*-(4-fluorophenyl)ureido, *N'*-ethyl-*N'*-(3-cyanophenyl)ureido, and the like.

"Monoalkylureidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-N(H)R_a or a radical of the formula -R_a- N(R_a)-C(O)-NH_2 where R_a is an alkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N'*", *e.g* , *N'*-methylureidomethyl, 2-(*N'*- ethylureido)ethyl, 1-(*N'*-propylureido)ethyl, *N*- methylureidomethyl, 2-(*N*-ethylureido)ethyl, 1-(*N*-propylureido)ethyl, and the like

"Monohaloalkylureidoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-N(H) R_f or a radical of the formula -R_a -N(R_f)-C(O)-NH_2 where R_a is an alkyl radical as defined above and R_f is a haloalkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N'*", *e.g* , *N'*- chloromethylureidomethyl, 2-(*N'*-(2,2-difluoroethyl)ureido)ethyl, 1- (*N'*-(3-chloropropyl)ureido)ethyl, *N*-(trifluoromethyl) ureidomethyl, 2-(*N*-(pentafluoroethyl)ureido)ethyl, 1-(*N*-(3- iodopropyl)ureido)ethyl, and the like.

"Monoarylureidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-N(H) R_b or a radical of the formula -R_a -N(R_b)-C(O)-NH_2 where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N'*", *e g* , *N'*-phenylureidomethyl, 2-(*N'*-(4- methoxyphenyl)ureido)ethyl, 1-(*N'*-(3-chlorophenyl)ureido)ethyl, *N*-phenylureidomethyl, 2-(*N*-(2-trifluoromethylphenyl)ureido) ethyl, 1-(*N*-(4-chlorophenyl)ureido)ethyl, and the like

"Monoaralkylureidoalkyl" refers to a radical of the formula -R_a -N(H)-C(O)-N(H)R_d or a radical of the formula -R_a-N(R_d)-C(O)-NH_2 where R_a is an alkyl radical as defined above and R_b is an aralkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N'*", *e g* , *N'*-benzylureidomethyl, 2-(*N'*-(4-methoxybenzyl)ureido)ethyl, 1-(*N'*-(3-

chlorobenzyl)ureido)ethyl, *N*- benzylureidomethyl, 2- (*N*-(2-trifluoromethylbenzyl)ureido)ethyl, 1-(*N*-(4- chlorobenzyl)ureido)ethyl, and the like.

"Monophenylamino" refers to an amino radical substituted by a phenyl radical as defined herein.

"Monophenylalkylamino" refers to an amino radical substituted by a phenylalkyl group as defined below, *e g* , benzylamino, 2-(benzyl)butylamino, and the like.

"Monophenylaminoalkyl" refers to an alkyl radical as defined above substituted by a monophenylamino group as defined above, *e.g.*, (phenytamino)methyl, 2-(1-(phenyl)ethylamino) ethyl, and the like

"Monophenylalkylaminoalkyl" refers to an alkyl radical as defined above substituted by a monophenylalkylamino group as defined above, *e.g* , (benzylamino)methyl, 2-(2-benzyl)butylamino)ethyl, and the like

"Nitro" refers to the radical $-NO_2$.

"Oxo" refers to the subsituent =O

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution

"Phenyl" refers to the benzene radical optionally substituted by one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, alkenyl, nitro, cyano, amino, monoalkylamino, dialkylamino, alkylcarbonyl, carboxy, alkoxycarbonyl, and aminocarbonyl

"Phenoxy" refers to the radical of the formula $-OR_h$ where R_h is phenyl as defined above.

"Phenylalkyl" refers to an alkyl radical as defined above substituted by a phenyl radical, *e g* , benzyl, and the like

"Phenylalkenyl" refers to an alkenyl radical as defined above substituted by a phenyl radical, *e.g* , 3-phenylprop-2-enyl, and the like

"Phenylalkoxy" refers to a radical of the formula $-OR_i$ where R_i is a phenylalkyl radical as defined above, *e g* , benzyloxy, and the like

"Phenylalkoxyalkyl" refers to an alkyl radical as defined above substituted by a phenylalkoxy radical as defined above, *e g* , benzyloxymethyl, and the like

"Phenylcarbonyl" refers to a radical of the formula -C(O)-R_h where R_h is a phenyl radical as defined above, *e g* , (4-chlorophenyl) carbonyl, (4-fluorophenyl)carbonyl, and the like

"Phenylaminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_h where R_h is a phenyl radical as defined above, *e g* , (4-chlorophenyl)aminocarbonyl, (4-methoxyphenyl)aminocarbonyl, and the like

"Pharmaceutically acceptable counterion" " refers to those anions which retain the biological effectiveness and properties of the parent compound. which are not biologically or otherwise undesirable. Examples of such anions may be found in Berge, S M *et al* , *Journal of Pharmaceutical Sciences* (1977), Vol 66, No 1, pp. 1-19

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, pyruvic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, zinc, aluminum salts and the like Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2- diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*- ethylpiperidine, polyamine resins and the like

Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine

"THF" refers to tetrahydrofuran

"Therapeutically effective amount" refers to that amount of a compound of formula (I) which, when administered to a human female in need of such administration, is sufficient to effect treatment, as defined below, for endometriosis which are alleviated by the CCR-1 antagonist activity. The amount of a compound of formula (I) which constitutes a "therapeutically effective amount" will vary depending on the compound, the disorder and its severity, and the age of the human female to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure

"Treating" or "treatment" as used herein cover the treatment of endometriosis disorder in a human female, and include:

(i) preventing the disorder from occurring in a human female, in particular, when such human female is predisposed to the disorder but has not yet been diagnosed as having it,

(ii) inhibiting the disorder, *i e*, arresting its development, or

(iii) relieving the disorder, *i e.*, causing regression of the disorder

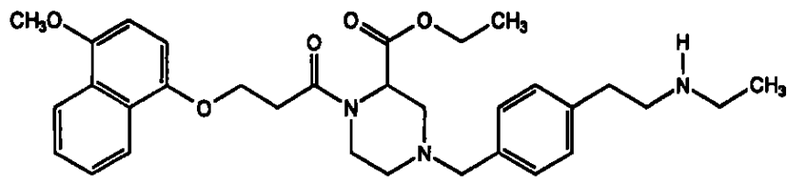
"Ureido" refers to a radical of the formula -N(H)-C(O)-NH_2

"Ureidoalkyl" refers to a radical of the formula -R_a-N(H)C(O)NH_2 where R_a is an alkyl radical as defined above, *e g*, ureidomethyl, 2- (ureido)ethyl, 3-(ureido)propyl, and the like.

It is understood from the above definitions and examples that for radicals containing a substituted alkyl group any substitution thereon can occur on any carbon of the alkyl group

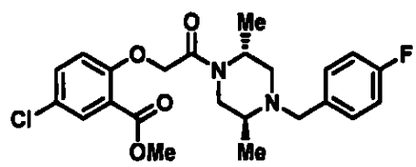
The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms in their structure The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of this invention Absolute configuration of certain carbon atoms within the compounds, if known, are indicated by the appropriate absolute descriptor *R* or *S* The descriptor "*trans*" is used to indicate that the R^{1a} or the R^{1b} substituents are on opposite sides of the piperazine plane The descriptor "*cis*" is used to indicate that the R^{1a} or the R^{1b} substituents are on the same side of the piperazine plane.

The nomenclature used herein is a modified form of the I.U P. A C system wherein the compounds of the invention are named as piperazine derivatives. For example, a compound of formula (Ia) wherein R^6 is -C(O)-, R^5 is ethylene, R^4 is -O-, R^{1a} is in the 2-position of the piperazine ring and is ethoxycarbonyl, R^2 is 2-(ethylamino)ethyl in the 4-position of the phenyl ring and R^3 is naphthalen-1-yl substituted at the 4-position by methoxy, *i e* , the compound of the following formula·



is named herein as 1-(2-((4-methoxynaphthalen-1-yl)oxy)ethyl)carbonyl-2-ethoxycarbonyl-4-(4-(2-(ethylamino)ethyl)benzyl)piperazine or with the nomenclature according to the following example:

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester



Utility and Administration

A. Utility

The CCR1 antagonists according to the present invention are potent inhibitor of disease score in animal models and cell culture models of endometriosis

The compounds of the invention inhibit the chemokine (MIP-1α and RANTES) induced migration of monocytes and macrophages and are therefore useful in the treatment and prevention of endometriosis in human females

Clinical studies are performed to investigate the benefit of the CCR1 antagonists according to the present invention in the treatment and prevention of endometriosis.

B. Testing

To demonstrate that the compounds inhibit the activity of MIP-1α or RANTES several assays may be employed One assay utilizes a microphysiometer, which uses a patented silicon-based light addressable potentiometric sensor to continuously monitor subtle changes in extracellular pH levels. These changes result from the generation of acidic metabolites excreted by living cells into their immediate microenvironment during basal and stimulated conditions It has been previously demonstrated by microphysiometry that THP-1 cells, which have been shown to express the chemokine receptors, CCR1 and CCR2, respond dose-responsively to their respective chemokines, including MIP-1α, RANTES and MCP-1 (a ligand for CCR2). See, *e.g.*, Hirst, M *et al*, "Chemokine receptors," *Journal of NIH Research* (1995), Vol 80. Another assay which may be used to demonstrate the ability of the compounds to inhibit the activity of MIP- 1α and RANTES is based on the measurement of intracellular Ca^{2+} concentrations and/or increases in intracellular [^{3}H] inositol phosphate release from MIP-1α and RANTES stimulated cells Ligand binding to the CCR1 receptor results in G- protein induced activation of phospholipase C, which leads to the conversion of phosphatidyl inositol phosphate to inositol phosphate and diacyglycerol. Inositol phosphate in turn binds to a receptor located at intracellular sites to release Ca^{2+} into the cytoplasm In addition to Ca^{2+} concentration increases due to release from intracellular stores, binding of inositol phosphate to its receptor leads to an increased flux of extracellular calcium across the membrane and into the cell Thus the activation of the CCR1 receptor by MIP-1α and RANTES and, subsequently, inhibition of the activation by the compounds of the invention can be determined by assaying for an increase in free intracellular Ca^{2+} levels Typically this can be achieved by the use of calcium-sensitive fluorescent probes such as quin-2, fura-2 and indo-1. Alternatively, functional activation or inhibition of the activation of the CCR1 receptor can be measured by quantitation of [^{3}H] inositol phosphate release from the cell pre-labeled with [^{3}H] inositol.

Standard *in vitro* binding assays may be employed to demonstrate the affinity of the compounds for the CCR1 receptor (thereby inhibiting the activity of MIP- 1α and RANTES by competitive binding to the receptor) See, *e g.*, Neote, K *et al*, Cell (1993), Vol. **72**, pp 415-425 One particular assay employs the use of HEK293 cells which have been stably transfected to express human CCR1 receptor

Endometriosis cell culture models with human U937 cells and primary human peritoneal macrophages in combination with a peritoneal fluid pool from patients with endometriosis are used as tools to investigate the effects of CCR1 antagonists on inhibition and reduction of chemokine induced monocites/macrophages migration

Determination of CCR1 mRNA in endometrial and endometriotic tissue samples can be performed for example by real-time quantitative RT-PCR analysis

Standard *in vivo* assays which may be employed to demonstrate the compounds usefulness in the treatment of endometriosis is for example the animal model of surgically induced endometriosis in intact cycling rats as also reported in the literature (15)

Other very important models to assay the compounds usefulness *in vivo* in the treatment of endometriosis are models in primates.

In comparison to rodents, primates (Baboon, Cynomolgous, Rhesus monkeys) have a menstrual cycle, are continuos breeders and develop spontaneous endometriosis. In addition, endometriosis can also be induced for example by the inoculation of menstrual tissue or by autologous transplantation of endometrial tissue into the peritoneal cavity (9, 10). Furthermore it is possible to isolate and characterize their pentoneal fluid

Own experimental data show for example that non human primates express the receptor CCR1 As in human, it could be shown that CCR1 is localized on tissue infiltrating immune cells in endometriotic lesions /grafts. By immunohistochemical staining and cell counting it could be demonstrated, that the number of CCR1-positive cells is up-regulated in endometriotic grafts of Rhesus monkey (see Figure 6) The advantage of the non human primate model is the morphology of endometriotic lesions (red lesions, white lesions, endometrioma) resembling those found in women and reflecting the human situation Studies in non human primate are performed to evaluate activity of CCR1 antagonist according to the present invention.

C. General Administration

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out *via* any of the accepted modes of administration or agents for serving similar utilities Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, sublingually, intramuscular, subcutaneously, intravaginally or intravenously in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the

invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of one or more suitable pharmaceutical excipient(s). Preferably, the composition will be about 5% to 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease- state to be treated For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, is formed by the incorporation of any of the normally employed excipients Such excipients include non- toxic and chemically compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers, and the like, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, cyclodextrin, propyl gallate, and the like Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like, a disintegrant such as croscarmellose sodium or derivatives thereof, a lubricant such as magnesium stearate and the like, and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like

The compounds of the invention, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0 5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, *e g.*, polyoxyethylene glycols and polyethylene glycols (PEG), *e g* , PEG 1000 (96%) and PEG 4000 (4%), and propylene glycol

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., a compound(s) of the invention (about 0 5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in

a carrier, such as, for example, water, saline, aqueous dextrose, aqueous cyclodextrin, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art, for example, see *Remington's Pharmaceutical Sciences,* 18th Ed , (Mack Publishing Company, Easton, Pennsylvania, 1990) The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of edometriosis alleviated by the inhibition of the activity of the chemokines, MIP-1α and RANTES.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the seventy of the particular disease- states, and the host undergoing therapy.

Generally, a therapeutically effective daily dose is from about 0 014 mg to about 14 0 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof, preferably, from about 0 14 mg to about 10 0 mg/kg of body weight per day; and most preferably, from about 1 4 mg to about 7 0 mg/kg of body weight per day For example, for administration to a 70 kg person, the dosage range would be from about 1 0 mg to about 1 0 gram per day of a compound of the invention, or a pharmaceutically acceptable salt thereof, preferably from about 10 mg to about 700 mg per day, and most preferably from about 100 mg to about 500 mg per day

Description of the drawings

Other features and advantages of the invention will become apparent from the following description of some favourable forms of embodiment of the invention, provided purely as a non-restricting example, with reference to the accompanying drawings, in which

Figure 1 shows the localization of CCR1 in endometriotic lesions and endometrial tissue

In endometriotic-peritoneal lesions the chemokine receptor CCR1 is localized on tissue infiltrating immune cells (A-D) CCR1 expressing immune cells were not detected in endometrium of patients with endometriosis (E) as well as in endometrium of non endometriotic controls (G). Negative control (F, H).

Figure 2 shows analysis data of CCR1 mRNA expression in endometriotic lesions and endometrium from patients with endometriosis
Controls line 1, 2 and 3 represent endometrium from non endometriotic women In these tissue samples the CCR1 mRNA expression is low Lanes 4-9 are tissue samples from women with endometriosis.
In brackets· endometrium and endometriotic lesion from the same patient
The CCR1 mRNA expression is up-regulated in endometriotic lesions (lines 5, 7, 9) in comparison to the samples of endometrium (lines 4, 6, 8)

Figure 3 shows the characterization of immune cells expressing CCR1
Co-immunostainings with monoclonal antibodies for CCR1 (Fig. A and D), CD4 (Fig 4 B) and CD68 (Fig 4 E) confirm that the chemokine receptor CCR1 is expressed on monocytes, and macrophages (CD 68) T helper cells (CD4) (Fig 4 C and F).

Figure 4 shows the effects of the CCR1 antagonist on area and volume of peritoneal endometriotic lesions in rats with experimental induced endometriosis
Controls· White bar animals were treated 4 weeks with vehicle, propylene glycol (0 5 mg/kg) Dotted bar Animals received an anti estrogen (11β-Fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10thia-6azapentadecyl)-estra-1,3,5(10)-triene-3,17β-diol) (1 mg/kg). Striped bar· Treatment of animals with a CCR1 antagonist according to the present application and particularly with (2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as sulphate salt (50 mg/kg) In comparison to the vehicle control, the data show that compounds according to the present invention reduce effects on area and volume of peritoneal endometriotic cysts in rat

Figure 5a and 5b CCR1 mRNA expression in endometriosis rat model

Figure 5a shows the expression of CCR1 mRNA in endometriotic cysts of mesenterium and pentoneum Operated rat uterus and rat ovary were used as controls (1-3 animal 1, 4-7 animal 2) In comparison to uterus and ovary, CCR1 mRNA expression is up-regulated in cysts of peritoneum and mesenterium

Figure 5b shows the expression of CCR1 ligand RANTES in treated and untreated animals Control group (untreated animals)· RANTES is highly expressed in mesenteral and peritoneal lesions The treatment with CCR1 antagonists induces after 3 weeks of treatment a significant downregulation of RANTES mRNA in peritoneal and mesenterial cysts of rat Results represent mean values from three animals

Figure 6 a and 6b Number and localization of CCR1 stained cells in endometrium and endometriotic grafts / lesions of Rhesus monkey

Figure 6A· CCR1 positive cell counts The cell counts represent the average number of CCR1 positive cells per section counted with an ocular grid The cells were identified by immunohistochemical staining Six sections were counted n=3 animals The number of CCR1 expressing cells is up-regulated in endometriotic grafts during the menstrual cycle in rhesus monkey

Figure 6b Localisation of CCR1 stained cells in endometriotic grafts/ lesions and in endometrium In comparison to the endometrium, the number of CCR1 expressing cells is enhanced in endometriotic grafts/lesions

Preferred Embodiments

One aspect of the invention are the compounds of formula (Ia) as defined above in the Summary of the Invention Of these compounds, a preferred group of compounds of formula (Ia) is that group of compounds wherein

R^3 is

a carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, arylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, hydroxyalkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy,

aminoalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy) cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy) aralkyl, (monoalkylamino)aralkyl, (hydroxyalkyl)hioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkylamino, heterocyclylamino, (cycloalkylalkyl)amino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl) aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, (hydroxyalkoxy)carbonyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, dialkylaminocarbonyloxyalkyl, alkylcarbonylalkyl, arylcarbonylalkyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, (aminocarbonylalkyl) aminocarbonyl, (monoalkylaminocarbonylalkyl) aminocarbonyl, (carboxyalkyl) aminocarbonyl, (alkoxycarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, *monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino,* hydroxyamidino, guanidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, monohaloalkylureido, (monoalkyl)(monoaryl)ureido, dialkylureido, diarylureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl) ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl) glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido,

(alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, glycinamidoalkyl, alaninamido, monoalkylalaninamido, alaninamidoalkyl, heterocyclyl and heterocyclylalkyl

Of this group of compounds, a preferred subgroup of compounds is that group of compounds wherein

R^4 is

-O-, -N(R^7)- or -C(R^8)-,

R^5 is

an alkylene chain,

R^7 is

selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, aralkylcarbonylamino, (aralkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, aralkylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, (aralkylcarbonyl)(alkyl)aminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, dialkylureido ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, and dialkylaminocarbonylalkyl

Of this subgroup of compounds, a preferred class of compounds is that group of compounds wherein.

R^4 is

-O-,

R^5 is

methylene, and

R^6 is

-C(O)-.

Of this class of compounds, a preferred subclass of compounds is that group of compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo,

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, aminoalkoxy, cycloalkyl, cycloalkylaminoalkyl, aralkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkylalkyl)aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy)carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl) aminocarbonyl,

(aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonylalkyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido (monoarylaminocarbonyl) (alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

Preferred compounds within this subclass of compounds are selected from the group consisting of the following compounds

(2*S*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1- ((phenoxy)methyl)carbonyl-2-ethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- (methoxymethyl)piperazine,

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-((acetylamino)methyl)piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((4-fluorobenzyl)amino)ethyl)4- (4-fluorobenzyl)piperazine,

1-((4-chlorophenoxy)methyl)carbonyl- 2-(2-((methyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine,

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methyl-5- methylpiperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(ethoxycarbonyl)piperazine,

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(methoxycarbonyl)methylpiperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((methoxy) methyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-(methoxy)ethyl)piperazine,

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl) piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxypropyl)piperazine,

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-hydroxybut-4-ynyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(2-hydroxyethyl)piperazine ;

1-((4- chlorophenoxy)methyl)carbonyl-3-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine,

(*cis*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine,

(2*S*, 5*R*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(2*S*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2,5-dimethylpiperazine,

(2*R*,5*S*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(2-methylthio)ethylpiperazine,

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy) methylpiperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((2-hydroxyethyl)thio) methyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-(*N'*-(ethoxycarbonylmethyl) ureido)methyl)piperazine;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-((amino)carbonyloxy)methyl-4-(4-fluorobenzyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((acetyl) methyl)piperazine,

(2*R*,5*R*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl) piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxybutyl)piperazine,

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)-5-((diethylamino)methyl)piperazine,

(2*R*, 5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) -5-((dimethylamino)methyl)piperazine,

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine,

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1- yl)methyl)piperazine;

(*cis*)-1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine,

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6- dimethylpiperazine,

1-((phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

1-((2-(acetylamino)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxypropyl)-4-(4-fluorobenzyl) piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut-3-enyl)-4-(4-fluorobenzyl)piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-3- trifluoromethyl-4-(4-fluorobenzyl)piperazine, and

(*trans*)- 1-((4-chloro-2-((4-(2,5-di(trifluoromethyl)phenylcarbonyl)piperazin-1-yl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

Of this subclass of compounds, a preferred group of compounds is that group of compounds wherein

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, hydroxyalkyl, hydroxyalkenyl, cyanoalkyl, alkoxyalkyl, monoalkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, aryloxyalkylcarbonyloxyalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, alkyl, alkoxy, formyl, nitro, cyano, aminoalkoxy, cycloalkylaminoalkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl,

alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl)aminoalkyl alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy) carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido, (monoarylaminocarbonyl) (alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

Preferred compounds within this group of compounds in this subclass group of compounds are selected from the group consisting of the following compounds

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;
1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;
4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-ethylpiperazine;
(2*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-propylpiperazine;
(2*S*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine,
4-(4-fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl) spiro[cyclopropane-1,2'-piperazine],
1-((4-chlorophenoxy)methyl) carbonyl-2-hydroxymethyl-4-(4-fluorobenzyl)piperazine;
4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-(methoxy)ethyl) piperazine,
1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2- methylpropyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine,
1-((4- chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine,
1-((4-chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5- methylpiperazine;
(2*R*)-1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine,
(2*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- (hydroxymethyl)piperazine,
4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine,
4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(((methyl)ureido) methyl)piperazine;
(2*R*,3*R*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine;
(*cis*)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4- fluorobenzyl)piperazine;
4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5- methylpiperazine,
(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((hydroxy)methyl)piperazine,
(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((methoxy)methyl)piperazine,
(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine,
(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxyethyl)piperazine;
(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyprop-3-enyl)piperazine;
(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine;
(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl) piperazine,
(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl)piperazine;
(3*S*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3,5-dimethylpiperazine; 1-((4-chloro-3-nitrophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;
(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,
(*trans*)-1-((4-chloro-2- (diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,
(*trans*)-1-((4-chloro-2-hydroxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,
(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((ethyl) (1-methylbutyl)aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(benzylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((1-methylbutyl)amino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*iso*- propylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-nitrophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-methylphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (acetylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(1-(phenylsulfonyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- ((methyl)(ethyl)amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(1- (dimethylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(2*R*)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(oxazol-2-ylaminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2- (morpholin-4-ylmethyl)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-bromo-2-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro-2-methoxycarbonylphenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2- aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(*trans*)-1-((4-methyl-2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-methyl-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine·

(*trans*)-1-((3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-nitro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl- 2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((5- nitro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-acetyl-4,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl)piperazine;

(*trans*)-1-((4- methyl-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((3-chloro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2- (2-azidoethyl)-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(phthalimido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(maleimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((4- (benzylcarbonyl)piperazin-1-yl)methyl)phenoxy)methyl)-carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((4-((2,3,4-trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(2,6-difluorophenyl)ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (ethenylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (cyclopropylcarbonylamino)phenoxy)methyl)carbonyl-2 5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (cyclopentylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((furan-2- yl)carbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methoxyphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*- (methoxycarbonylmethylcarbonyl)-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(2-methoxycarbonylethyl)carbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl) aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(3-trifluoromethyl-4-fluorophenyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(4-methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-chlorophenyl)carbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(4-fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(2,3- difluorophenylcarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-diflurophenylcarbonyl)glycinamido) phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((ethoxycarbonylmethylcarbonyl) aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(3- chloropropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'* -(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((3-fluorophenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'* -(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(2*S*)-1-((4-chloro- 2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, and

(*trans*)-1-((4-chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine

A more preferred group of compounds in this subclass group of compounds are those compounds wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl and hydroxyalkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxy, formyl, nitro, cycloalkylaminoalkyl, hydroxyalkyl, amino, alkylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, alkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, hydroxyamidino, ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, alaninamido, and heterocyclylalkyl.

Preferred compounds within this more preferred group of compounds in this subclass group of compounds are selected from the group consisting of the following compounds:

(*trans*)-1-((4- chloro-3-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(2*R*,5*S*)-1-((4-chloro-2-(aminocarbonyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2 *S*,5*R*)-1-((4-bromo-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1- ((3-hydroxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*S*,5*R*)-1-((4-nitro-3- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(2R)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(2-hydroxyethyl)piperazine,

(*trans*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine,

(2*R*,5*S*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine,

(*trans*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(2*R*,5*S*)-1-((4-chloro- 3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine,

(2*R*,6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,6-dimethylpiperazine;

(*trans*)-1-((4-chloro-2- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine,

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-hydroxyethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro-2- (acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino- 4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(2- (methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2R)-1-((4-chloro-2-(glycinamido) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- ((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-ethylureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-amino-5-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt;

(*trans*)-1-((4-chloro-2- (((ethyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(((diethyl)amino) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(((cyclopropyl)amino)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((dimethyl)amino)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((methyl)amino)methyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4- methylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(1-(methylamino)ethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(methylsulfonyl)(methyl)aminoethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(2*R*,5 *S*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(imidazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(triazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(tetrazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- ((morpholin-4-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(2*R*)-1-((4-chloro-2- aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine,

(2*R*,5*S*)-1-((4- chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1- ((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- ((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2- aminoethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-aminocarbonylphenyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (hydroxyamidino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(*N'*-(methoxymethylcarbonyl)glycinamido)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonylaminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

The most preferred group of compounds within this subclass group of compounds are those compounds wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4- position with chloro and at the 2-position by aminocarbonyl, ureido, or glycinamido., namely, the compounds selected from the group consisting of the following compounds.

(2*R*,5*S*)- 1-((4-chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1- ((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(2*R*,5*S*)-1-((4-chloro-2- (ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(2*R*,5*S*)-1-((4-chloro-2-(glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

Of the subgroup of compounds as set forth above, another preferred class of compounds are those compounds wherein

R^4 is

-N(R^7)-;

R^5 is

methylene,

R^6 is

-C(O)-, and

R^7 is

selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl

Of this class of compounds, a preferred subclass of compounds are those compounds wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo,

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, aminoalkoxy, cycloalkyl, cycloalkylaminoalkyl, aralkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl) aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy)carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonylalkyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl) glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl

A preferred group of compounds in this subclass group of compounds is that group wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, hydroxyalkyl, hydroxyalkenyl, cyanoalkyl, alkoxyalkyl, monoalkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, aryloxyalkylcarbonyloxyalkyl, and heterocyclylalkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, alkyl, alkoxy, formyl, nitro, cyano, aminoalkoxy, cycloalkylaminoalkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl)aminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy) carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido, (monoarylaminocarbonyl) (alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl

A more preferred group in this subclass group of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl and hydroxyalkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxy, formyl, nitro, cycloalkylaminoalkyl, hydroxyalkyl, amino, alkylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, alkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, hydroxyamidino, ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, alaninamido, and heterocyclylalkyl

An even more preferred group of compounds in this subclass group of compounds are those compounds wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido Preferred compounds in this group selected from the group consisting of the following compounds

(*trans*)-1-((4-chlorophenylamino)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

1-((4-chloro-2-(aminocarbonyl) phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, and

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine,

Of the subgroup of compounds as set forth above, another preferred class of compounds are those compounds wherein

R^4 is

$-C(R^8)_2-$,

R^5 is

methylene,

R^6 is

-C(O)-, and

each R^8 is

independently selected from the group consisting of hydrogen, alkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, ureidoalkyl, monoalkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, and dialkylaminoalkyl.

A preferred subclass of compounds of this class of compounds are those compounds wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo,

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, aminoalkoxy, cycloalkyl, cycloalkylaminoalkyl, aralkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl) aminoalkyl, (cycloalkyalkyl)aminoalkyl,

alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy)carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonylalkyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl

A preferred group of compounds within this preferred subclass of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, hydroxyalkyl, hydroxyalkenyl, cyanoalkyl, alkoxyalkyl, monoalkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, aryloxyalkylcarbonyloxyalkyl, and heterocyclylalkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, alkyl, alkoxy, formyl, nitro, cyano, aminoalkoxy, cycloalkylaminoalkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino,

alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl)aminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy) carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

A more preferred group of compounds within this subclass of compounds are those compounds wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl and hydroxyalkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxy, formyl, nitro, cycloalkylaminoalkyl, hydroxyalkyl, amino, alkylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, alkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, hydroxyamidino,

ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, alaninamido, and heterocyclylalkyl.

An even more preferred group of compounds of this subclass group of compounds are those compounds wherein

R^2 is

4-fluoro,

R^3 is

phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido; and

one R^8

is hydrogen and the other R^8 is selected from the group consisting of amino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, ureidoalkyl, monoalkylureidoalkyl, monohaloalkylureidoalkyl, and aminoalkyl

Preferred compounds in this even more preferred group are those compounds selected from the group consisting of the following compounds.

(*trans*)-1-(2-(4-chlorophenyl)-3-(methylsulfonylamino)propyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2- (methylsulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(acetylamino) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2-(amino)ethyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)- 2-(ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(ureido)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4- chlorophenyl)-3-(amino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*t*- butoxycarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2- ((ethoxycarbonylmethylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2- (*N'*-iso-propylureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(*N'*-(2- chloroethyl)ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-((2- nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2- ((2,4-dinitrophenyl)sulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2- (cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2-((2- cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- ((2-methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (*t*-butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (ethyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl) ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, and

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

Of the compounds of formula (Ia), another preferred group of compounds are those compounds wherein.

R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkylsufonyl, arylsulfonyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, haloalkoxy, alkenyl, alkynyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl) aminoalkyl, alkoxycarbonylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, guanidino, ureido, monoalkylureido, ureidoalkyl, monoalkylureidoalkyl, and glycinamido.

Of this group of compounds, a preferred subgroup of compounds is that group of compounds wherein

R^4 is

-O-, - N(R^7)- or -C(R^8)-,

R^5 is

an alkylene chain,

R^7 is

selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl; and

each R^8

is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, aralkylcarbonylamino, (aralkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, aralkylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, (aralkylcarbonyl)(alkyl)aminoalkyl,

arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, and dialkylaminocarbonylalkyl.

Of this subgroup of compounds, a preferred class of compounds are those compounds wherein

R^4 is

-O-,

R^5 is

methylene, and

R^6 is

-C(O)-

Of this class of compounds, a preferred subclass group of compounds are those compounds wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl, and

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo

A preferred group of compounds in this preferred subclass group of compounds are those compounds wherein R^3 is selected from the group consisting of azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-

oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperidinyl, piperazinyl, 4-pipendonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone

A more preferred group of compounds in this preferred subclass of compounds are those compounds wherein R^3 is benzopyranyl, benzopyranonyl, benzfuranyl, benzofuranonyl, quinolinyl, indolyl, indolinyl, oxazolyl, imidazolyl, or benzothienyl

A preferred compound in this more preferred group is (*trans*)-1-((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine

Another aspect of the invention is a method of treating edometriosis in a human female, which method comprises administering to a human female in need of such treatment a therapeutically effective amount of a compound of formula (Ia) as described above.

Preparation of Compounds of The Invention

The following Reaction Schemes are directed to the preparation of compounds of formula (Ia) It is understood that those compounds of the invention which are not specifically prepared in the following Reaction Schemes may be prepared by similar synthetic processes with the appropriately substituted starting materials and reagents. It is also understood that in the following descriptions, combinations of the various substituents (*e g.* , R^{1a}, R^2 and R^3 substituents) on the depicted formulae are permissible only if such combinations result in stable compounds

For the purposes of convenience only, preparation of compounds of the invention where R^3 is only phenyl are illustrated below. It is understood that other R^3 groups (including other carbocyclic and heterocyclic ring systems) may be prepared in a similar manner

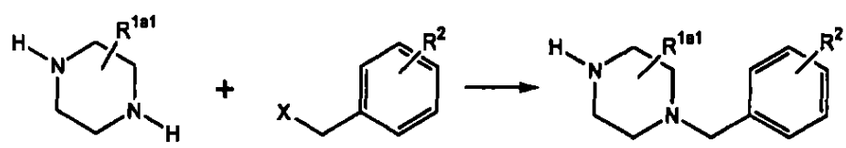
It is also understood that during the preparation of the compounds of the invention, as described below, additional reactive groups (for example, hydroxy, amino or carboxy groups) on the intermediate compounds utilized in the preparation may be protected as needed by the appropriate protecting group by treating the intermediate compound prior to the desired reaction with the appropriate protecting group precursor by methods known to those of ordinary skill in the art The protecting groups may then be removed as desired by methods known to those of ordinary skill in the art, for example, by acidic or basic hydrolysis Such protecting groups and methods are described in detail in Greene, T W and Wuts, P G M , "Protective Groups in Organic Synthesis", 2nd

Edition, 1991, John Wiley & Sons Also, dimethylpiperazines can be prepared in an asymmetric synthesis according to the method outlined in Mickelson, J W., Belonga, K L , Jacobsen, E J , *Journal of Organic Chemistry* (1995), Vol. 60, pp. 4177-4123 It should be noted that the only difference in the two groups of compounds covered by formula (Ia) and formula (Ib) as described below is the required substitution of the piperazine ring in the compounds of formula (Ia) Accordingly, it is understood that, unless otherwise indicated, the following Reaction Schemes directed to the preparation of the compounds of formula (Ib) may be used to prepare compounds of formula (Ia) .

A. Preparation of Compounds of Formula (C)

Compounds of formula (C) are intermediates in the preparation of the compounds of the invention. They are prepared according to the following Reaction Scheme 1 wherein R^{1a1} is one or more independently selected R^{1a} substituents as described above in the Summary of the Invention for compounds of formula (Ia) (except that R^{1a1} can not be aminoalkyl or monoalkylaminoalkyl unless appropriately protected); X is chloro, bromo or iodo, and R^2 is as described above for compounds of formula (Ia)

Reaction Scheme 1



(A) (B) (C)

The compounds of formula (A) and formula (B) are commercially available, *e.g.*, from Aldrich Chemical Co or Sigma Chemical Co , or may be prepared according to methods known to those of ordinary skill in the art.

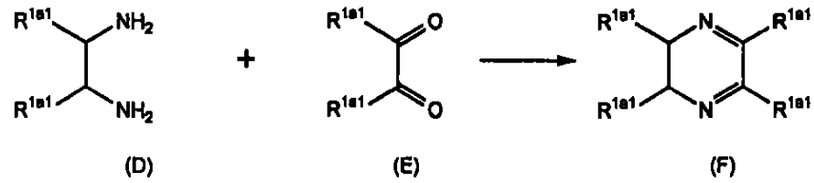
In general, the compounds of formula (C) are prepared by treating a compound of formula (A) in an organic solvent, such as methylene chloride, with an equimolar amount of a compound of formula (B) The reaction mixture is stirred for about 10 to 20 hours at ambient temperature. The reaction mixture is then concentrated to afford a residue which is dissolved in an organic solvent. The compound of formula (C) is isolated from the solution by standard isolation techniques, for example, by filtration, concentration and flash column chromatography

B. Preparation of Compounds of Formula (Ga) and Formula (Gb)

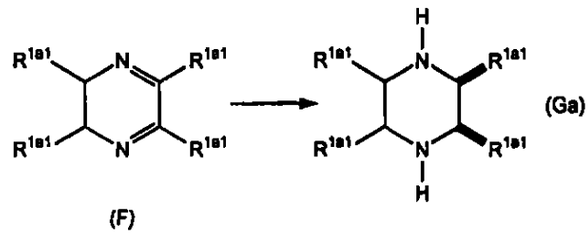
Compounds of formula (Ga) and formula (Gb) are intermediates in the preparation of compounds of the invention They are prepared as illustrated in the following Reaction Scheme 2 wherein each R^{1a1} is independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy) aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, alkoxycarbonylaminoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, alkoxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, heterocyclyl and heterocyclylalkyl (except that R^{1a1} can not be aminoalkyl or monoalkylaminoalkyl unless appropriately protected)

Reaction Scheme 2

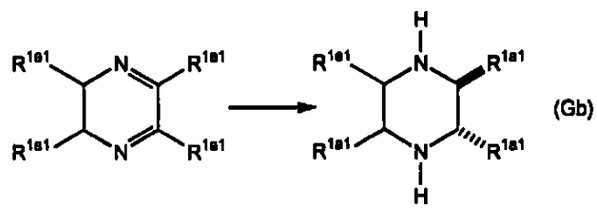
1



2a



2b



Compounds of formula (D) and formula (E) are commercially available, *e g* , from Aldrich Chemical Co or Sigma Chemical Co , or may be made from methods known to those of ordinary skill in the art.

In general, compounds of formula (Ga) *and formula* (Gb) *are prepared by first treating* a compound of formula (D) in an anhydrous aprotic solvent, such as anhydrous ether, with an equimolar amount of a compound of formula (E) in an anhydrous aprotic solvent, such as anhydrous ether, over a period of time, for example, over a two hour period The resulting reaction mixture is stirred for about 2 to about 4 hours, preferably for about 3 hours, at ambient temperature The compound of formula (F) is isolated from the reaction mixture by standard isolation techniques, such as concentration of the product and purification by vacuum distillation

To a solution of a strong reducing agent, such as lithium aluminum hydride, in an anhydrous polar aprotic solvent, such as tetrahydrofuran, is added the compound of formula (F) The resulting mixture is stirred at ambient temperature for about 30 minutes to about 2 hours, preferably for about 1 hour The mixture is then heated to

reflux to complete the reaction Upon completion, the compound of formula (Ga) is isolated from the reaction mixture by standard isolation techniques, such as quenching by water and a mild base, followed by filtration.

Alternatively, to a solution of formula (F) in a polar protic solvent, such as absolute ethanol, is added a solid alkaline metal, such as sodium metal over a period of time, such as over a 3 hour period The resulting mixture is heated to reflux for about 2 to about 4 hours, preferably for about 3 hours The compound of formula (Gb) is distilled from the reaction mixture by the addition of water to the reaction mixture The distillate is then treated with an aqueous acid, such as hydrochloric acid, to form the salt of the compound of formula (Gb)

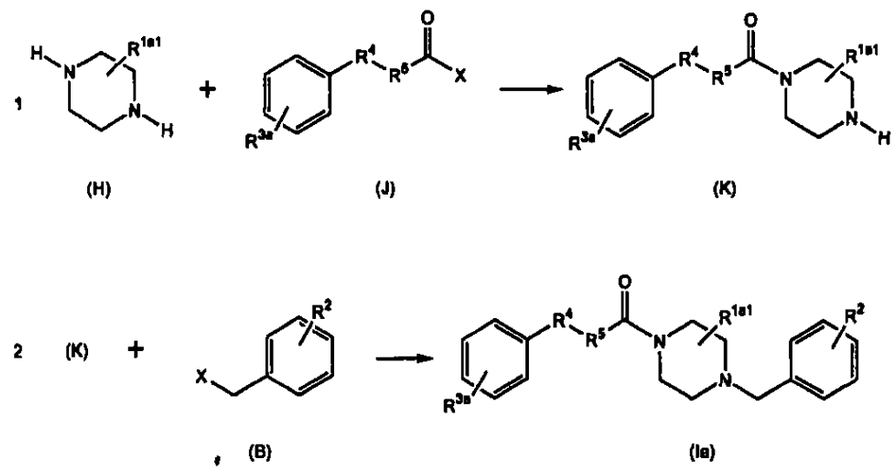
Compounds of formula (Ga) and formula (Gb) may then be treated with compounds of formula (B) in a manner similar to that described above in Reaction Scheme 1 to produce compounds of the invention wherein the relative orientation of the R^{1a} substituents is fixed

C. Preparation of Compounds of Formula (Ia)

The compounds of formula (Ia) are compounds of the invention and they are prepared as illustrated in the following Reaction Scheme 3 wherein each X is independently chloro or bromo, R^{1a1} is one or more independently selected R^{1a} substituents as described above in the Summary of the Invention for compounds of formula (Ia) (except that R^{1a1} can not contain a primary or secondary amine unless appropriately protected), R^2, R^4 and R^5 are as described in the Summary of the Invention for compounds of formula (Ia) (except that R^4 and R^5 can not contain a primary or secondary amine unless adequately protected), and R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cyctoalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl carboxy, alkoxycarbonyl,

aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl, and R^4 and R^5 are as described above in the Summary of the Invention.

Reaction Scheme 3



The compounds of formula (B), formula (H) and formula (J) are commercially available, for example, from Aldrich Chemical Co or Sigma Chemical Co , or may be prepared according to methods known to those of ordinary skill in the art

In general, compounds of formula (Ia) are prepared by the foregoing Reaction Scheme by first treating a compound of formula (H) in a polar solvent, such as methanol, with an equimolar amount of a compound of formula (J) in an anhydrous polar solvent, such as anhydrous ether The resulting reaction mixture is stirred at ambient temperature for about 5 minutes to about 24 hours in the presence of an acid-scavenging base, such as triethylamine The compound of formula (K) is then isolated from the reaction mixture by standard isolation techniques, such as organic phase extraction, evaporation of solvents and purification by flash column chromatography

The compound of formula (K) in an aprotic polar solvent, such as tetrahydrofuran, is treated with an excess molar amount of a compound of formula (B) in the presence of a mild base, such as triethylamine and, optionally, a catalytic amount of sodium iodide The resulting mixture is stirred at ambient temperature for about 1 to 5 days, preferably for about 2 days. The compound of formula (Ia) is then isolated from the reaction mixture by standard isolation techniques such as filtration, concentration of volatiles and purification by flash column chromatography.

Alternatively, compounds of formula (Ga) and formula (Gb), as prepared above in Reaction Scheme 2, may be used in place of compounds of formula (H) in this Reaction Scheme to produce compounds of the invention wherein the relative orientation of the R^{1a} substituents is fixed

D. Preparation of Compounds of Formula (Ia)

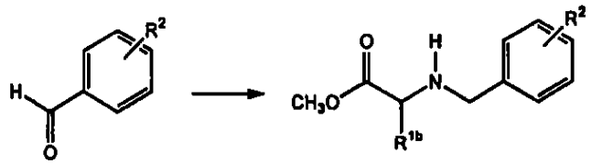
Compounds of formula (Ia) are compounds of the invention and they are prepared as illustrated in the following Reaction Scheme 4 wherein X is chloro, bromo or an activated ester, P^1 and P^2 are independently nitrogen-protecting groups, such as *t*-butoxycarbonyl (P^1 can also be hydrogen); R^{1a}, R^2, R^4 and R^5 are as described above in the Summary of the Invention, R^{1b} is as described above in the Summary of the Invention for compounds of formula (Ic) and (Id), and R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl,

dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl

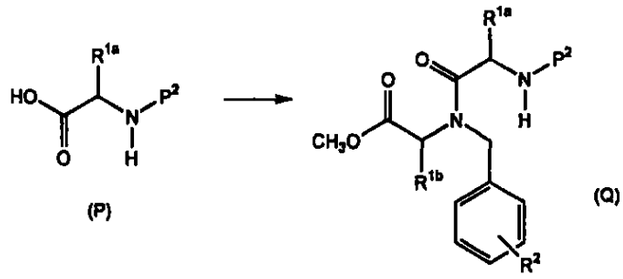
Reaction Scheme 4

1

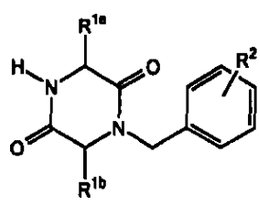
(L) (M)

2 (M) + 

(N) (O)

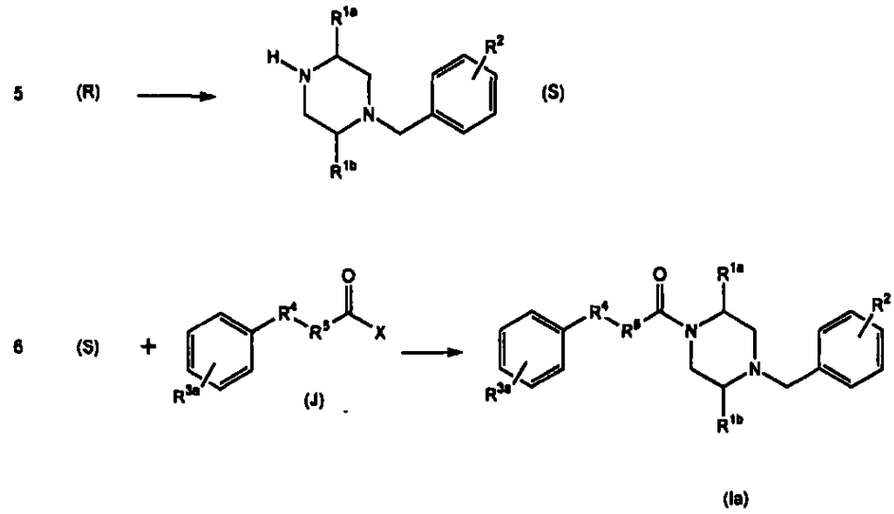
3 (O) + 

(P) (Q)

4 (Q) 

(R)

Reaction Scheme 4 continued



Compounds of formula (L), formula (N), formula (P) and formula (J) are commercially available, for example, from Aldrich Chemical Co. or Sigma Chemical Co., or may be prepared according to methods known to one of ordinary skill in the art

Compounds of formula (L) wherein the R^{1b} substituent contains an un-protected hydroxy group may be protected with the appropriate oxygen-protecting group prior to the synthesis of the compound of formula (M) Removal of the protecting group may be performed as desired

In general, the compounds of formula (Ia) are prepared by first esterifying a compound of formula (L) by treating the compound with an excess molar amount of a lower alkanol, preferably methanol, in the presence of an acid, preferably hydrochloride gas, at about 0°C to ambient temperature The resulting mixture is then stirred at about 0°C to reflux temperature, preferably at ambient temperature, for about 4 hours to about 18 hours The mixture is then concentrated by removal of solvents to produce the compound of formula (M) .

To a solution of the compound of formula (M) in an organic solvent, such as methanol, at about 0°C to ambient temperature, is added an excess molar amount of a compound of formula (N), and then treated with a mild acid, such as acetic acid, and stirred at ambient temperature for about 2 hours to about 4 hours, preferably for about 3 hours, to form an intermediate imine The imine is then reduced *in situ* by treatment with a reducing agent, such as sodium cyanoborohydride, to produce a compound of formula

(O), which is isolated from the reaction mixture by standard isolation techniques, such as filtration and purification by flash column chromatography

To a solution of a compound of formula (P) in a polar aprotic solvent, such as anhydrous tetrahydrofuran, is added an acid scavenging mild base, such as *N*-methylmorpholine, followed by the addition of an acid coupling reagent, such as isobutylchloroformate The resulting mixture is stirred at about 0°C to ambient temperature for about 15 minutes to about 2 hours, preferably for about 15 minutes at 0°C and then for about an hour at ambient temperature, to form an intermediate active ester of the compound of formula (P). The intermediate is then treated *in situ* with a compound of formula (O) in anhydrous polar aprotic solvent, such as anhydrous tetrahydrofuran and the resulting mixture is stirred at ambient temperature for about 10 hours to about 24 hours, preferably for about 15 hours. The compound of formula (Q) is isolated from the reaction mixture by standard isolation techniques, such as concentration, organic phase separation and purification by flash column chromatography

The compound of formula (Q) in an aprotic solvent, such as methylene chloride, at about 0°C, is then treated with a strong organic acid, such as trifluoroacetic acid. for a period of about 2 to about 4 hours, preferably for about 2 hours, to remove the protecting group on the nitrogen atom, followed by spontaneous cyclization to form the compound of formula (R), which is isolated from the reaction mixture by standard isolation techniques, such as neutralization with a mild base, filtration and concentration.

The compound of formula (R) in an anhydrous polar aprotic solvent, such as anhydrous tetrahydrofuran, at about 0°C is treated with a strong reducing agent, such as lithium aluminum hydride The resulting mixture is then heated to reflux for about 12 hours to about 24 hours, preferably for about 15 hours. The mixture is then cooled to ambient temperature and the reaction quenched with water, followed by aqeous base, preferably aqueous potassium hydroxide. The resulting mixture is allowed to stir at ambient temperature for about 30 minutes to an hour. The compound of formula (S) is then isolated from the reaction mixture by filtration and concentration

The compound of formula (S) in a polar aprotic solvent, such as methylene chloride, in the presence of excess amount of an acid scavenging base, such as triethylamine, is added a slighly excess molar amount of a compound of formula (J) in a polar aprotic solvent, such as methylene chloride The resulting mixture is stirred at ambient temperature for about 15 minutes to about 1 hour, preferably for about 15 minutes The compound of formula (Ia) is then isolated from the reaction mixture by standard

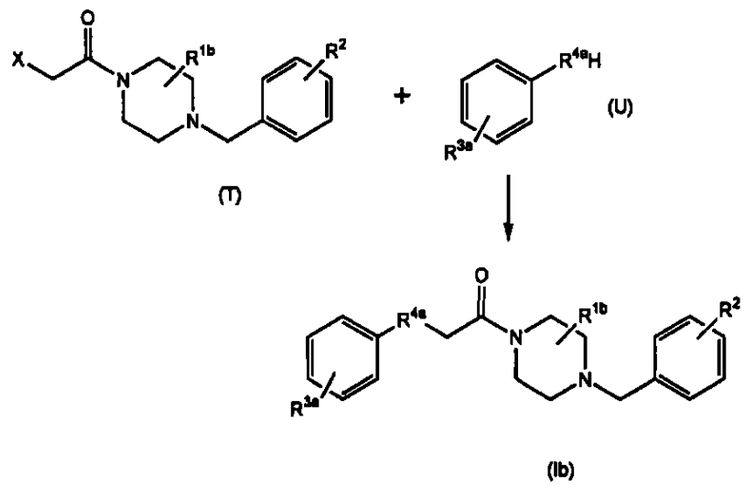
isolation techniques, such as extraction, concentration and flash column chromatography

E. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) are prepared as illustrated below in Reaction Scheme 5 where X is chloro or bromo, R^{1b} is as described above in the Summary of the Invention for R^{1a} of compounds of formula (Ia) and hydrogen, and R^2 is as described above in the Summary of the Invention for compounds of formula (Ia), R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, aryloxy, haloalkyl, formyl, nitro, cyano, aralkoxy, haloalkoxy, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, cycloalkylaminoalkyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, aryloxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, arylsulfonyl, hydroxyalkoxy, aminoalkoxy, (monoalkylamino)aralkyl, aminoalkylamino, heterocyclylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, arylcarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, heterocyclylaminoalkyl, (hydroxyalkoxy)carbonyl, (aminocarbonylalkyl)aminocarbonyl, (monoalkylaminocarbonylalkyl) aminocarbonyl, (carboxyalkyl)aminocarbonyl, (alkoxycarbonylalkyl) aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonyloxyalkyl, monoarylureido, monoaralkylureido, monohaloalkylureido, (monoalkyl)(monoaryl)ureido, diarylureido, (haloalkylcarbonyl)ureido, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, (alkoxyalkylcarbonyl)glycinamido, aminocarbonylglycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido, (monoarylaminocarbonyl) (alkyl)glycinamido, glycinamidoalkyl, alaninamido,

monoalkylalaninamido, alaninamidoalkyl, heterocyclyl and heterocyclylalkyl, and R^{4a} is -O- or -N(R^{7a})- where R^{7a} is hydrogen, alkyl, aryl or aralkyl

Reaction Scheme 5



Compounds of formula (U) are commercially available, for example, from Aldrich Chemical Co or Sigma Chemical Co., or may be prepared according to methods known to those of ordinary skill in the art. Compounds of formula (T) may be prepared according to the methods described herein for compounds of formula (C) or for compounds of formula (K), or by acylating the compounds of formula (C) as prepared herein by standard methods known to those of ordinary skill in the art

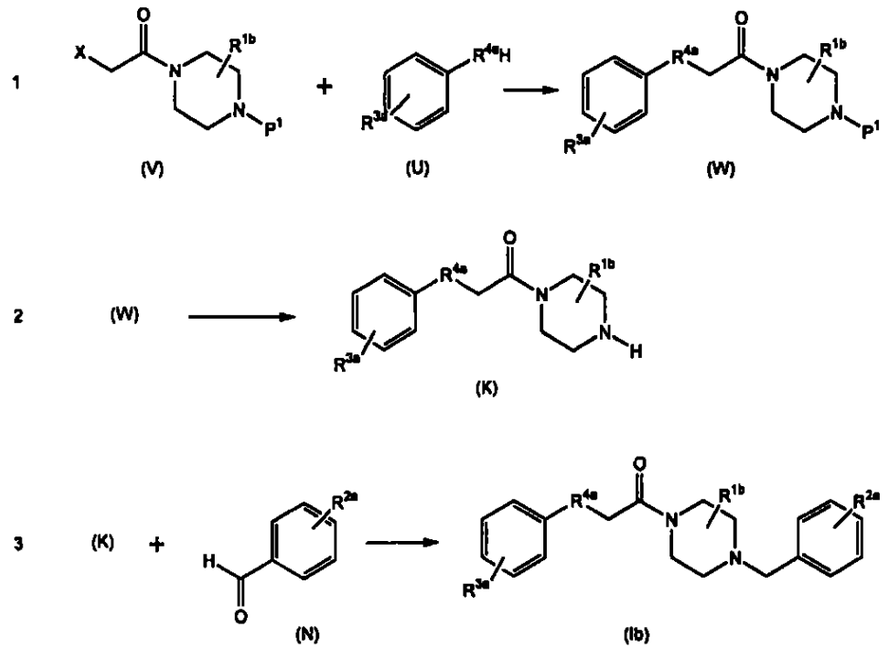
In general, the compounds of formula (Ib) are prepared by the foregoing Reaction Scheme by first treating a compound of formula (T) in an anhydrous aprotic solvent, such as anhydrous dimethylformamide, with a slightly excess molar amount of a compound of formula (U) in the presence of a mild base, such as potassium carbonate. The resulting mixture is stirred at about 50°C for about 10 hours to about 24 hours, preferably for about 15 hours The compound of formula (Ib) is then isolated from the reaction mixture by standard isolation techniques, such as extraction, filtration and precipitation

F. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) may also be prepared as illustrated in the following Reaction Scheme 6 where X is chloro, bromo or an activated ester, P^1 is a nitrogen-

protecting group, such as t- butoxycarbony, R^{1b} is as described above in the Summary of the Invention for compounds of formula (Ic) and formula (Id), R^{2a} is as described above in the Summary of the Invention for R^2 in compounds of formula (Ic) except that R^{2a} can not be formyl or formylalkyl, R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl, and R^{4a} is -O- or -N(R^{7a})- where R^{7a} is hydrogen, alkyl, aryl or aralkyl.

Reaction Scheme 6



Compounds of formula (U) and formula (N) are commercially available, for example, from Aldrich Chemical Co. or Sigma Chemical Co , or may be prepared according to methods known to those of ordinary skill in the art. Compounds of formula (V) may be prepared according to the method described above for compounds of formula (K) in Reaction Scheme 3.

In general, compounds of formula (Ib) as prepared in the foregoing Reaction Scheme 6 are prepared by first treating a compound of formula (U) in an aprotic solvent, such as dimethylformamide, at about 0°C, with a strong base, such as potassium hexamethyldisilazide, to deprotonate the compound The resulting mixture is stirred for about 20 minutes to an hour, preferably for about 20 minutes, at about 0°C. An equimolar amount of a compound of formula (V) in an aprotic solvent, such as dimethylformamide is then added to the mixture and the resulting mixture is stirred at ambient temperature for about 1 to 24 hours, preferably for about 2 hours. The compound of formula (W) is then isolated from the reaction mixture by standard isolation techniques, such as extraction and concentration

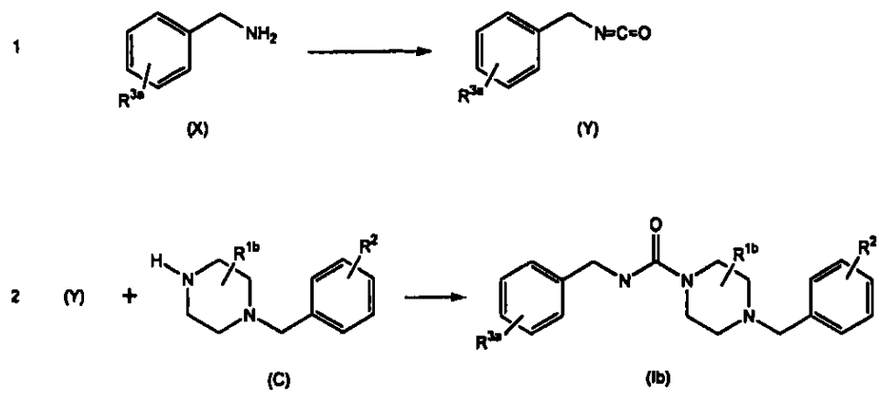
The P^1 protecting group is then removed from the compound of formula (W) to form a compound of formula (K) by standard amine-deprotecting procedures, such as treating the compound of formula (W) with a strong acid, such as trifluoroacetic acid.

To a solution of the compound of formula (K) in a polar solvent, such as methanol, at about 0°C to ambient temperature, was added an excess molar amount of a compound of formula (N) , and then treated with a mild acid, such as acetic acid, and stirred at ambient temperature for about 2 hours to about 4 hours, preferably for about 3 hours, to form an intermediate imine The imine is then reduced *in situ* by treatment with a reducing agent, such as sodium cyanoborohydride, to produce a compound of formula (Ib), which is isolated from the reaction mixture by standard isolation techniques, such as filtration and purification by flash column chromatography.

G. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) may also be prepared as illustrated in the following Reaction Scheme 7 where R^{1b} is as described above in the Summary of the Invention for compounds of formula (Ic) and formula (Id); and R^2 is as described above in the Summary of the Invention for the compounds of formula (Ib); and R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl

Reaction Scheme 7



Compounds of formula (X) are commercially available, for example, from Aldrich Chemical Co or Sigma Chemical Co , or may be prepared acccording to methods known to those of ordinary skill in the art Compounds of formula (C) may be prepared according to methods described herein.

In general , the compounds of formula (Ib) prepared by this Reaction Scheme are prepared by first treating a compound of formula (X) in an organic solvent, such as toluene. with phosgene for a period of time from about 1 hour to about 24 hours, preferably for about 2 hours, at reflux temperature to form the isocyanate of formula (Y), which is isolated from the reaction mixture by standard isolation techniques, such as concentration and filtration

The compound of formula (Y) in an anhydrous aprotic polar solvent, such as tetrahydrofuran, is then treated with an equimolar amount of a compound of formula (C). The resulting mixture is stirred at ambient temperature for about 10 hours to about 48 hours, preferably for about 20 hours. The compound of formula (Ib) is then isolated from the reaction mixture by standard isolation techniques, such as concentration and evaporation of solvents.

In addition to the foregoing Reaction Schemes 1 through 7, other compounds of invention may be made by reactions known to one skilled in the art For example, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein at least one R^{1a} substituent or at least one R^{1b} substituent is selected from the group consisting of hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, hydroxyalkylthioalkyl, and hydroxyalkylaminoalkyl, may be dissolved in an aprotic polar solvent, such as methylene chloride, in the presence of a mild acid scavenging base and then treated

with a slightly excess molar amount of a sulfonyl halide, such as sulfonyl chloride, to form an intermediate compound containing a sulfonate leaving group The compound may then be dissolved in an anhydrous aprotic solvent, such as dimethylformamide, and treated, in the presence of a mild base, with the appropriate nucleophilic reagent to form compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein the R^{1a} substituent or the R^{1b} substituent (depending on the nucleophilic reagent utilized) may be selected from the group consisting of heterocyclylalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, cycloalkylamino, cyanoalkyl, (cycloalkylalkyl)aminoalkyl, or hydroxyalkylthioalkyl

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains a hydroxy group, such as hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy) aralkyl, (hydroxy) cycloalkylalkyl, hydroxyalkylthioalkyl, and hydroxyalkylaminoalkyl, may be treated with a mild oxidizing agent, such as oxalyl chloride, which is dissolved in an inert organic solvent, such as methylene chloride, to which DMSO is added over a period of time at about -60°C to about 0°C, preferably at about -50°C The reaction mixture is stirred at about -60°C to about 0°C for about 15 minutes to about an hour, preferably for about 15 minutes, and then a mild base, such as triethylamine, is added to the mixture The mixture is allowed to gradually warm to ambient temperature, at which point the oxidized compound (*i e* , the corresponding aldehyde) of formula (Ia), or any appropriately substituted starting material or intermediate thereof, is isolated from the reaction mixture by standard isolation techniques

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an aldehyde or a ketone group, such as formyl, alkylcarbonyl or alkylcarbonylalkyl, may be treated with the appropriate organometallic reagent, such as an organomagnesium or organolithium, under standard Grignard synthesis reaction conditions to form the corresponding hydroxy-substituted compounds

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains a hydroxy group, such as hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy) aralkyl, (hydroxy)cycloalkylalkyl, hydroxyalkylthioalkyl, and hydroxyalkylaminoalkyl, in an anhydrous polar solvent, such as anhydrous ether, in the presence of a strong base, such as sodium hydride, may be treated with an alkyl halide, such as methyl iodide, at ambient temperatures, to form the corresponding alkoxy-substituted compounds

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein at least one R^{1a} substituent or at least one R^{1b} substituent is formyl or formylalkyl, may be reacted with a primary or secondary amine, under the reductive amination conditions as described above for the preparation of the compounds of formula (O) or the compounds of formula (Ib) as prepared in Reaction Scheme 6 to form the corresponding compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein the R^{1a} substituent or the R^{1b} substituent is monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl, or hydroxyalkylaminoalkyl

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an ester group, such as an alkoxycarbonyl, aryloxycarbonyl or aralkoxycarbonyl group, may be subjected to standard basic hydrolysis conditions, to form the corresponding compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an acid group, *i e* a carboxy group.

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is -C(O)- may be reduced to the corresponding compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is $-CH_2-$ by methods known to those of ordinary skill in the art, for example, by the method described above for compounds of formula (S)

In addition, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is -C(O)- may be converted to a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is -C(S)- by treatment with Lawesson's Reagent under standard conditions known to those of ordinary skill in the art

In addition, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain an unoxidized sulfur atom may be oxidized with the appropriate sulfur oxidizing agent according to methods known to those skilled in the art, such as using hydrogen peroxide, to produce the corresponding compounds which contain a sulfinyl or a suffonyl group in place thereof

Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a carboxy group can be converted to compounds containing the corresponding amide group by first converting the carboxy group into an activated ester or mixed anhydride using, for example, isobutyl chlorofarmate in the presence of a mild base, such as *N*- methylmorpholine, in an

aprotic solvent, such as THF, and then treating the ester with the appropriately substituted primary or secondard amine in an aprotic solvent, such as THF.
Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a cyano group can be converted to the compounds containing a hydroxyamidino group by reaction with the an hydroxyamine in a polar solvent, such as DMSO. The hydroxyamine may be prepared *in situ* by first treating the hydrochloride salt of the hydoxyamine with a base, such as triethylamine.
Alternatively, of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a hydroxy group may be converted to the compounds containing the corresponding azide group by treating the compound with triphenylphosphine and an alkyl azodicarboxylate, for example diethylazodicarboxylate, in an aprotic solvent, such as THF, and then displacing the activated oxygen so formed with an azide source, such as diphenylphosphorylazide, in an aprotic solvent, such as THF.
Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a $-NH_2$ group or a $-R_a-NH_2$ group may be converted to compounds containing a corresponding $-R_a-N(H)-C(O)-$ group by reacting the compound with appropriately substituted acid halide under standard acylation conditions
Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a acid halide group (-C(O)-X where X is halo) or an activated ester group can be converted to compounds containing the corresponding -C(O)-N(H)- group by reacting the compound with the appropriately substituted primary or secondardy amine under standard acylation or amide bond formation conditions
Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an primary or secondary amine group can be converted to compounds containing the corresponding aminoalkyl group in a manner similar to the conversion of formula (M) to formula (O) in Reaction Scheme 4
In particular, the amine is reacted with an appropriately substituted aldehyde to form the intermediate imine, which is then reduced by treatment with an appropriate reducing agent, such as sodium cyanoborohydride.
Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a primary or secondary amine can be converted to the compounds containing the corresponding ureido group by reacting the compound with phosgene in a manner similar to Reaction Scheme 7 above (in an

aprotic solvent) to form the corresponding isocyanate, which is then reacted with the appropriately substituted primary or secondary amine

In addition, all compounds of the invention that exist in free base form or free acid form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic acid, or by the appropriate inorganic or organic base Salts of the compounds of the invention can also be converted to the free base form or to the free acid form or to another salt by methods known to those skilled in the art

The following specific Preparations and Examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention

In the following Preparation and Examples, all NMR data refers to ^{1}H NMR spectrum data and is given in the format of "(multiplicity, number of hydrogens)" The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield

PREPARATION 1

Compounds of Formula (C)

A To a solution of 2-methylpiperazine (0 10 g, 1 mmol) in CH_2Cl_2 (2 mL) was added 4-fluorobenzyl bromide (0 125 mL, 1 mmol). The resultant mixture was stirred at ambient temperature After 15 hours, the mixture was concentrated *in* vacuo to afford a solid. This solid was dissolved in CH_2Cl_2 and washed sequentially with water, aqueous $NaHCO_3$ solution, then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to an oil Purification by flash column chromatography afforded 0.025 g (12% yield) of 1-(4-fluorobenzyl)-3-methylpiperazine, a compound of formula (C), as a colorless oil, NMR ($CDCl_3$) 7.3 (m, 2), 7 0 (m, 2), 3.4 (s, 2), 3 0-2 6 (m, 5), 2 0 (br s, 2), 1 6 (t, 1), 1 0 (d, 3) ppm

B In a similar manner, the following compounds of formula (C) were made:

(2*R*,5*S*)-1-(chloro)acetyl-4-(4-fluorobenzyl)-2,5- dimethylpiperazine-1-(4-fluorobenzyl)piperazine,

(*trans*)- 1-(4-fluorobenzyl)-2,5-dimethylpiperazine,

(*cis*)-1-(4- fluorobenzyl)-2,3-dimethylpiperazine;

(*trans*)-1-(4- fluorobenzyl)-2,3-dimethylpiperazine, and

(*cis*)-1-(4- fluorobenzyl)-3,5-dimethylpiperazine

C In a similar manner, other compounds of formula (C) are made

PREPARATION 2

Compounds of Formula (F)

A. To a solution of ethylene diamine (13 g, 216 mmol) in anhydrous ether (600 mL) was added 2,3-butanedione (18 6 g, 216 mmol, in 200 mL anhydrous ether) dropwise over 2 hours. The resulting mixture was stirred at ambient temperature After 3 hours, the clear solution was concentrated *in vacuo* to afford a brown oil Purification by vacuum distillation afforded 16 6 g (70% yield) of 5,6-dimethyl-2,3-dihydropyrazine, a compound of formula (F), as clear, yellow oil; b p 60°C /16 mm Hg, NMR ($CDCl_3$) 3 3 (br s, 4), 2 1 (s, 6) ppm

B In a similar manner, other compounds of formula (F) are made.

PREPARATION 3

Compounds of formula (Ga)

A To a solution of lithium aluminum hydride (0 36 g, 10 mmol) in anhydrous tetrahydrofuran (50 mL) was carefully added 5,6-dimethyl-2,3- dihydropyrazine (1 0 g, 9 mmol, in 10 mL of anhydrous tetrahydrofuran). The resulting mixture was stirred at ambient temperature for 1 hour, then heated to reflux After the reaction was completed, as determined by thin layer chromatographic analysis of reaction mixture, the reaction mixture was cooled to ambient temperature and quenched by sequential addition of 0 4 mL of water, 0.4 mL of 15% aqueous NaOH solution, then 1 2 mL of water After brief shaking, the mixture was filtered through a fritted funnel Filtrate was concentrated *in vacuo* to 0 92 g (90% yield) of (*cis*)-2,3-dimethylpiperazine, a compound of formula (Ga), as clear, yellow oil; NMR ($CDCl_3$) 2 7 (m, 4), 2.5 (m, 2), 0 9 (d, 6) ppm

B. In a similar manner, other compounds of formula (Ga) are made

PREPARATION 4

Compounds of formula (Gb)

A. To a solution of 5,6-dimethyl-2, 3-dihydropyrazine (2.3 g, 21 mmol) in absolute ethanol (60 mL) was added sodium metal (6.5 g, 280 mmol) in small portions over a 3 hour period. The resulting mixture was heated to reflux After 3 hours at reflux, the product was distilled from the mixture while 200 mL of water was added gradually to reaction vessel The distillate was treated with 1 N aqueous HCl solution and concentrated *in vacuo* to afford a semi-solid Titration with acetone afforded 0.78 g (20% yield) of (*trans*)-2,3- dimethylpiperazine, a

compound of formula (Gb), as an orange solid; NMR (DMSO-d_6) 9 8 (br s, 4), 3 5-3.2 (m, 6), 1 2 (s, 6) ppm

B. In a similar manner, other compounds of formula (Gb) are made

PREPARATION 5

Compounds of Formula (K)

A To a solution of (*cis*)-2,6- dimethylpiperazine (0 115 g, 1.1 mmol) in methanol (35 mL) was added 4- chlorophenoxyacetyl chloride (0 205 g, 1.0 mmol, in solution of 6 mL of anhydrous ether). The resulting mixture was stirred at ambient temperature for 10 minutes and then triethylamine (0 10 mL, 0 72 mmol) was added After 30 minutes, the mixture was concentrated *in vacuo* to afford an oily residue This was taken up in ether and washed with saturated aqueous $NaHCO_3$ solution, then brine The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford an oil. Purification by flash column chromatography afforded 0 202 g (80% yield) of (*cis*)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine, a compound of formula (K), as a clear, colorless oil; NMR ($CDCl_3$) 7 3 (d, 2), 6 9 (d, 2), 4.7 (d, 1), 4 6 (d, 1), 4 4 (d, 1), 3.8 (d, 1), 2 7 (m, 3) , 2 2 (t, 1), 1.1 (m, 6) ppm

B In a similar manner, the following compounds of formula (I) were made (3*S*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-3,5- dimethylpiperazine; and (3*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine.

C In a similar manner, other compounds of formula (K) are made

PREPARATION 6

Compounds of Formula (M)

A. A solution of (2*R*)-3-benzyloxy-2-(*N* -(*t*-butoxycarbonyl)amino) propanoic acid (23 g, 78 mmol, $[\alpha]_D$ -4.4° (c = 2, H_2O)) in methanol (250 mL) was cooled to 0°C and HCl (g) bubbled into the solution until saturated The resulting mixture was stirred at ambient temperature for 17 hours and then concentrated *in vacuo* to afford 17 g (100% yield) of (2*R*)-3-benzyloxy-2-aminopropanoic acid methyl ester, a compound of formula (M), as a white solid; NMR (DMSO- d_6) 8.7 (br s, 3), 7 4-7.3 (m, 5), 4 5 (q, 2), 4 4 (br s, 1), 3 8 (s, 2), 3.7 (s, 3) ppm.

B In a similar manner, other compounds of formula (M) are made

PREPARATION 7

Compounds of Formula (O)

A. A solution of (2*R*)-3-benzyloxy-2- aminopropanoic acid methyl ester (19 g, 78 mmol) in methanol (350 mL) under N_2 was cooled to 0°C and acetic acid (2 g, pH 2) was added, followed by the addition of 4-fluorobenzaldehyde, a compound of formula (N) (12 5 mL, 117 mmol) and sodium cyanoborohydride (7 3 g, 117 mmol) and 3 Å molecular sieves (15 g). The resulting mixture was stirred at ambient temperature for 3 hours, then filtered through Celite (MeOH) The filtrate was concentrated *in vacuo* to afford a clear liquid. This was taken up in ethyl acetate and washed sequentially with 10% aqueous Na_2CO_3 solution, water, then brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* Purification by flash column chromatography on silica gel afforded 14 7 g (60% yield) of (2*R*)-3- benzyloxy-2-(*N*-(4-fluorobenzyl)amino)propanoic acid methyl ester, a compound of formula (O), as a clear, colorless oil, NMR ($CDCl_3$) 7 4-7 2 (m, 7), 7 0 (dd, 2), 4 5 (d, 2), 3 9-3.5 (m, 8) ppm, MS (LSIMS) 317

B In a similar manner, the following compounds of formula (O) were made

(2*R*)- 2-(*N*-(4-fluorobenzyl)amino)propanoic acid methyl ester,
(2*S*)-2-(*N*-(4-fluorobenzyl)amino)propanoic acid methyl ester,
(2*R*)-2-(*N*-(4-fluorobenzyl)amino)4- methylthiobutanoic acid methyl ester;
(2*R*)-2-(*N*-(4- fluorobenzyl)amino)-3-methoxypropanoic acid methyl ester,
(2 *R*)-2-(*N*-(4-fluorobenzyl)amino)-3-((2-hydroxyethyl)thio) propanoic acid methyl ester; and
(2*R*)-2-(*N*-(4- fluorobenzyl)amino)-3-methylbutanoic acid methyl ester

C In a similar manner, the following compounds of formula (O) are made

(2*S*)-2-(*N*-(4-fluorobenzyl) amino)-4-methylthiobutanoic acid methyl ester,
(2*S*)-2-(*N*-(4-fluorobenzyl)amino)-3-methoxypropanoic acid methyl ester,
(2*S*)-2(*N*-(4-fluorobenzyl)amino)-3-((2-hydroxyethyl)thio) propanoic acid methyl ester,
(2*S*)-2-(*N*-(4- fluorobenzyl)amino)-3-methylbutanoic acid methyl ester,
(2 *R*)-2-(*N*-(4-fluorobenzyl)amino)butanoic acid ethyl ester,
(2*S*)-2-(*N*-(4-fluorobenzyl)amino)butanoic acid ethyl ester,
(2*R*)-2-(*N*-(4-chlorobenzyl)amino)butanoic acid methyl ester;
(2*S*)-2-(*N*-(4-chlorobenzyl)amino) butanoic acid methyl ester;
(2*R*)-2-(*N*-(4- chlorobenzyl)amino)-4-methylthiobutanoic acid methyl ester,
(2 *R*)-2-(*N*-(4-chlorobenzyl)amino)-3-methoxypropanoic acid methyl ester;
(2*R*)-2-(*N*-(4-chlorobenzyl)amino)-3-((2- hydroxyethyl)thio)propanoic acid methyl ester, and
(2*R*)-2- (*N*-(4-chlorobenzyl)amino)-3-methylbutanoic acid methyl ester.

D In a similar manner, other compounds of formula (O) are made.

PREPARATION 8

Compounds of Formula (Q)

A To a solution of *N-t*-butoxycarbonyl-D-alanine (5.6 g, 30 mmol, $[\alpha]_D$ +23° (c=2, CH_3CO_2H)) in anhydrous tetrahydrofuran (150 mL) under N_2 at 0°C was added *N*-methylmorpholine (3.0 g, 30 mmol), followed by the addition of isobutylchloroformate (3.7 mL, 30 mmol) , resulting in the formation of a white solid The resulting suspension was stirred at 0°C for 15 minutes, and then at ambient temperature for 1 hour A solution of (2*R*)-3-benzyloxy-2-(*N*-(4-fluorobenzyl)- amino)propanoic acid methyl ester (7.5 g, 24 mmol, in 50 mL of anhydrous tetrahydrofuran) was added to the mixture and the resulting mixture was stirred at ambient temperature After 15 hours, the mixture was filtered through Celite (tetrahydrofuran). The filtrate was concentrated *in vacuo* to afford a yellow liquid, which was dissolved in ethyl acetate, washed with water and then with brine The organic phase was separated then dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by flash column chromatography on silica gel afforded 7 3 g (63% yield) of (2*R*)-3-benzyloxy-2-(*N*-(4- fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxy-carbonylamino) ethyl)carbonyl)amino)propanoic acid methyl ester, a compound of formula (Q), as a clear oil; NMR ($CDCl_3$) 7 4-7.2 (m, 7), 7 0 (dd, 2), 5 3 (d, 2), 4 9-4, 3 (m, 5), 4 1-3.7 (m, 4), 1 6 (s, 9), 1 0 (d, 3) ppm

B In a similar manner, the following compounds of formula (Q) were made·

(2*R*)-2-(*N*- (4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino) ethyl)carbonyl)amino)propanoic acid methyl ester,

(2*S*)-2- (*N*-(4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)propanoic acid methyl ester;

(2*R*)-2-(*N*-(4-fluorobenzyl)-*N*-(((1*R*)- 1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)propanoic acid methyl ester;

(2*S*)-2-(*N*-(4-fluorobenzyl)-*N*- (((1*R*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino) propanoic acid methyl ester;

(2*R*)-2-(*N*-(4- fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino) ethyl)carbonyl)amino)-4-methylthiobutanoic acid methyl ester,

(2*R*)-2-(*N*-(4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)-3-methoxypropanoic acid methyl ester,

(2*R*)-2-(*N*-(4- fluorobenzyl)- *N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)- 3-((2-hydroxyethyl)thio)propanoic acid methyl ester,

(2*R*)- 2-(*N*-(4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)-3-methylbutanoic acid methyl ester, and

(2*R*)-2-(*N*-(4-fluorobenzyl)-*N*- (((1*S*)-1-(*t*-butoxycarbonylamino)-2-(ethoxycarbonyl)ethyl)- carbonyl)amino)propanoic acid methyl ester.

C. In a similar manner, other compounds of formula (Q) are made

PREPARATION 9 Compounds of Formula (R)

A To a solution of (2*R*)-3-benzyloxy-2-(*N*-(4-fluorobenzyl)-*N*- (((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino) propanoic acid methyl ester (2 0 g, 4 mmol) in CH_2Cl_2 (25 mL) was cooled to 0°C and trifluoroacetic acid (25 mL) was added dropwise over 2 hours. At the end of the addition, the ice bath was removed and the mixture was stirred at ambient temperature. After 2 hours, the mixture was concentrated *in vacuo*. The residual yellow oil was taken up in ethyl acetate and washed with 1 N aqueous $NaHCO_3$ solution The organic layer was separated then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 1 2 g (83% yield) of (2*R*, 5*S*)-1-(4-fluorobenzyl)-2-(benzyloxy)methyl-5-methylpiperazine-3,6- dione, a compound of formula (R), as a clear oil, NMR ($CDCl_3$) 7 4-7 2 (m, 7), 7 0 (dd, 2), 5 0 (d, 1), 4.5-4.0 (m, 4), 3.9-3 5 (m, 4), 1 5 (d, 3) ppm, MS (LSIMS) 356.

B In a similar manner, the following compounds of formula (R) were made

(2*R*,5*S*)-1-(4-fluorobenzyl)-2,5-dimethylpiperazine-3,6- dione;

(2*S*,5*S*)-1-(4-fluorobenzyl)-2,5- dimethylpiperazine-3,6-dione;

(2*R*,5*R*)-1-(4- fluorobenzyl)-2,5-dimethylpiperazine-3,6-dione,

(2*S*,5 *R*)-1-(4-fluorobenzyl)-2,5-dimethylpiperazine-3,6-drone,

(2 *R*,5*S*)-1-(4-fluorobenzyl)-2-(2-methylthioethyl)-5- methylpiperazine-3,6-dione;

(2*R*,5*S*)-1-(4- fluorobenzyl)-2-(methoxymethyl)-5-methylpiperazine-3,6-dione,

(2*R*,5*S*)-1-(4-fluorobenzyl)-2-((2-hydroxyethyl)thiomethyl)-5- methylpiperazine-3,6-dione,

(2*R*,5*S*)-1-(4- fluorobenzyl)-2-(1-methylethyl)-5-methylpiperazine-3,6-dione; and

(2*R*,5*S*)-1-(4-fluorobenzyl)-2-methyl-5-(ethoxycarbonyl) methylpiperazine-3,6-dione

C In a similar manner, other compounds of formula (R) are made

PREPARATION 10

Compounds of Formula (S)

A To a suspension of (2*R*,5*S*)-1-(4- fluorobenzyl)-2-(hydroxy)methyl-5-methylpiperazine-3,6-dione (2 0 g, 7 5 mmol) in anhydrous tetrahydrofuran (50 mL) under N_2 at 0°C was carefully added lithium aluminum hydride (2.2 g, 60 mmol). The resulting suspension was heated to reflux After 15 hours, the mixture was cooled to ambient temperature and carefully quenched with water (2 mL) , then 1 N aqueous KOH solution (6 mL) The resulting suspension was stirred at ambient temperature for 30 minutes, then filtered through Celite (ethyl acetate) The filtrate was concentrated *in vacuo* to afford 1.6 g (90% yield) of (2*R*,5*S*)-1-(4-fluorobenzyl)-2- (hydroxy)methyl-5- methylpiperazine, a compound of formula (S), as a white solid; NMR ($CDCl_3$) 7 3 (dd, 2), 7 0 (dd, 2), 4 2-4 0 (m, 2), 3 5 (d, 1) 3.0 (m, 2), 2.7 (m, 2), 1 7 (m, 1), 1 0 (d, 3).

B In a similar manner, the following compounds of formula (S) were made:

(2*R*,5*S*)-1-(4- fluorobenzyl)- 2,5-dimethylpiperazine,
(2*S*,5*S*)-1-(4-fluorobenzyl)- 2,5-dimethylpiperazine,
(2*R*,5*R*)-1-(4-fluorobenzyl)- 2,5-dimethylpiperazine,
(2*S*,5*R*)-1-(4-fluorobenzyl)- 2,5-dimethylpiperazine,
(2*R*,5*S*)-1-(4-fluorobenzyl)- 2-(2-methylthioethyl)-5-methylpiperazine,
(2*R*,5*S*)- 1-(4-fluorobenzyl)-2-(methoxymethyl)-5-methylpiperazine;
(2 *R*,5*S*)-1-(4-fluorobenzyl)-2-((2-hydroxyethyl)thiomethyl)-5- methylpiperazine,
(2*R*,5*S*)-1-(4-fluorobenzyl)-2-(1- methylethyl)-5-methylpiperazine; and
(2*R*,5*S*)-1-(4- fluorobenzyl)-2-methyl-5-(ethoxycarbonyl)methylpiperazine

C. In a similar manner, other compounds of formula (S) are made

PREPARATION 11

Compounds of formula (W)

A. To a solution of 3,4,5-trimethoxyphenol (2.8 g, 15 mmol) in DMF (60 mL) at 0°C was added potassium hexamethyldisilazide (32 mL, 16 mmol, 0.5 M solution in toluene) The resulting mixture was stirred at 0°C. After 20 minutes, 1-(chloro)acetyl- 4-(*t*-butoxycarbonyl)piperazine (4 6 g, 15 mmol, in 15 mL of DMF) was added and the mixture stirred at ambient temperature. After 2 hours the mixture was poured into water and extracted with ethyl acetate The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 6 5 g (100% yield) of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(*t*-

butoxycarbonyl) piperazine, a compound of formula (W), as a yellow solid, NMR ($CDCl_3$) 7 2 (m, 2), 4 6 (s, 2), 3 8 (m, 9), 3 6 (m, 4), 3 4 (m, 4), 1.5 (s, 9) ppm.

B In a similar manner, the following compounds of formula (W) were made

1-((4- chlorophenyl)methyl)carbonyl-4-(*t*-butoxycarbonyl)piperazine,

(3*R*)-1-((4-chlorophenyl)methyl)carbonyl-3-methyl-4-(*t*-butoxycarbonyl)piperazine,

(3*S*)-1-((4-chlorophenyl)methyl) carbonyl-3-methyl-4-(*t*-butoxycarbonyl)piperazine; and

1- ((4-chlorophenyl)methyl)carbonyl-3-(2-((((4-chlorophenoxy)methyl)carbonyl) oxy)ethyl)-4-(*t*-butoxycarbonyl)piperazine

C In a similar manner, other compounds of formula (W) are made

PREPARATION 12 Compounds of formula (Y)

A To a solution of 4-chlorobenzylamine (0.50 g, 3 5 mmol) in toluene (15 mL) was added phosgene (7.3 mL, 14 mmol, 1.93 M solution in toluene). The resulting mixture was stirred at ambient temperature for 15 minutes, then heated to reflux After 2 hours at reflux, the mixture was cooled to ambient temperature and concentrated *in vacuo* to afford 0 70 g (100% yield) of 4-chlorobenzylisocyanate, a compound of formula (Y), as a yellow liquid; NMR ($CDCl_3$) 7 4-7 2 (m, 4), 4 4 (m, 2) ppm

B In a similar manner, other compounds of formula (Y) are made

EXAMPLE 1

Compounds of Formula (Ia) and Formula (Ib)

A To a solution of (2*R*,5*S*)-1-(4- fluorobenzyl)-2-(hydroxy)methyl-5-methylpiperazine (1 8 g, 6 7 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (excess) and 4-chlorophenoxyacetyl chloride (1 5 g, 7 4 mmol, dropwise in 10 mL solution of CH_2Cl_2) The resultant mixture was stirred at ambient temperature After 20 minutes, analysis by analytical TLC showed complete consumption of starting material had occurred The mixture was concentrated of volatiles *in vacuo* and the residue taken up in CH_2Cl_2 This was washed with saturated aqueous $NaHCO_3$ solution, then water, then brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* Purification by flash column chromatography on silica gel afforded 2 16 g (79% yield) of (2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((hydroxy) methyl)piperazine, as a solid yellow foam: NMR (DMSO-d_6) 7.7 (br s, 2), 7 3 (m, 4), 6 9 (d, 2), 5 0-4.2 (m, 5), 4 0-3 2 (m, 7), 1 2 (m, 3) ppm, MS (LSIMS) 406

B In a similar manner, other compounds of formula (Ia) were made·

1- ((4-chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5-methylpiperazine, trifluoroacetic acid salt, NMR (DMSO-d_6) 7.6 (m, 2), 7 3 (m, 4), 6 9 (m, 2), 5 0-3 8 (m, 6), 3.5-2 8 (m, 5), 1 4 (m, 3) ppm,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- ethylpiperazina;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-methylpiperazine,

4-benzyl-1-((4-chlorophenoxy)methyl) carbonyl-2-phenylpiperazine;

(2*R*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(1-methylethyl)piperazine;

4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(methoxymethyl) piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-ethylpiperazine-3-one;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-ethylpiperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4 6 (s, 2), 4 4 (m, 1), 3 7 (m, 1), 3 4 (m, 2), 2 8 (m, 2), 2 0-1 7 (m, 5), 0 9 (m, 3) ppm,

(2*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-methylpropyl)piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4 6 (m, 2), 4 2 (m, 1), 3 6-3 0 (m, 5), 2 7 (dd, 1), 2 2 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-benzylpiperazine;

4-(benzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-phenylpiperazine-3-one,

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4.7 (m, 3) , 3 8-3 2 (m,5), 2 8 (m, 2), 2 2 (m, 2), 2.0 (m, 2), 1.7 (m, 2) ppm;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl) carbonyl-2,6-dimethylpiperazine; NMR (DMSO-d_6) 7 6 (m, 2), 7 3 (m, 4), 6 9 (d, 2), 4 8 (m, 3), 4 4 (m, 3), 3 3 (d, 2), 3 0 (m, 2), 1 4 (m, 6) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(1-methylpropyl)piperazine,

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-methylpiperazine, hydrochloride salt,

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (m, 2), 4.2 (m, 1), 3 6-3 0 (m, 5), 2 7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0 9 (m, 3) ppm;

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-(2-methylpropyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(butyl)piperazine;

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6 9 (m, 2), 4 6 (m, 3), 3 5 (m, 5), 3 2 (dt, 1), 3.0 (m, 1), 2 8 (dd, 1), 2 2 (m, 2), 1 6 (m, 2), 1 0 (d, 3) ppm,

(2 *S*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2, 5-dimethylpiperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7.0 (t, 2), 6 9 (d, 2), 4 6 (m, 2), 4.2 (m, 1), 3 6-3 0 (m, 5), 2 7 (dd, 1), 2.2 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(2*S*,5*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine, hydrochloride salt, NMR (DMSO-d_6) 7 6 (m, 2), 7.2 (m, 4), 6 9 (d, 2), 4.8 (m, 2), 4.4 (m, 1), 4 1 (t, 1), 3 9-2 9 (m, 6), 1.5-1 2 (m, 6) ppm,

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine hydrochloride salt, NMR (DMSO-d_6) 7 6 (m, 2), 7.2 (m, 4), 6.9 (d, 2), 4 8 (m, 2), 4 4 (m, 1), 4 1 (t, 1), 3 9-2 9 (m, 6), 1 5-1 2 (m, 6) ppm,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(1,1-dimethylethyl)piperazine,

(2*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-methylpropyl)piperazine,

(2 *R*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- (2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5-methylpiperazine, NMR ($CDCl_3$) 7 2 (m, 6), 7 0 (m, 2), 6 8 (m, 4), 4.7-4 0 (m, 7), 3 6 (m, 2), 3 4 (m, 1), 3 1 (m, 1), 2 6 (m, 1), 2 3 (m, 2), 2 0 (m, 2), 1 0 (d, 3) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(methoxycarbonyl)methylpiperazine;

(2*S*)- 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine,

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl) carbonyl-2,3-dimethylpiperazine, hydrochloride salt, NMR (DMSO-d_6) 7.6 (m, 2), 7 2 (m, 4), 6.9 (m, 2), 5 0-4 1 (m, 6), 3 5-2 9 (m, 4), 1 5-1.2 (m, 6) ppm,

(2*R*)-4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-benzylpiperazine,

(2 *R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- propylpiperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4 6 (m, 2), 4 4 (m, 1), 3.7 (m,

1), 3 4 (m, 2), 3 0 (m, 1), 2 7 (m,2), 2 0-1 6 (m, 4), 1.2 (m, 2), 0.9 (m, 3) ppm ,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxyethyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (dd, 2), 4 7 (d, 2), 4 0-3 4 (m, 8), 2 8 (m, 2), 2.3 (m, 1), 1 8 (m, 3) ppm,

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(hydroxymethyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7.0 (t, 2), 6.9 (t, 2), 4.7 (d, 2), 3 9-3 2 (m, 7), 2 8-2 2 (m, 4) ppm,

(2*S*)-4-(4-fluorobenzyl)1- ((4-chlorophenoxy)methyl)carbonyl-2-butylpiperazine;

(2*R*, 6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine, hydrochloride salt, NMR ($CDCl_3$) 7 7 (br s, 2), 7 2 (m, 4), 6.8 (d, 2), 4.6 (s, 2), 4.4 (m, 3), 3 9 (m, 1), 3 5 (m, 1), 3 2 (m, 1), 2.8 (m, 2), 1 6 (s, 6) ppm,

(2*S*, 6*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine, hydrochloride salt; NMR ($CDCl_3$) 7 7 (br s, 2), 7 2 (m, 4), 6 8 (d, 2), 4 6 (s, 2), 4 4 (m, 3), 3.9 (m, 1), 3 5 (m, 1), 3 2 (m, 1), 2.8 (m, 2), 1 6 (s, 6) ppm;

4-(4- fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl)spiro[cyclopropane-1, 2'-piperazine], NMR ($CDCl_3$) 7.3 (m, 4), 7 0-6 8 (m, 4) , 4 6 (m, 4), 2.8 (m, 2), 2 2-1 6 (m, 4) ppm,

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-(trifluoromethyl)piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-5-(2-methylthio)ethylpiperazine, hydrochloride salt;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methylpiperazine,

(2*S*)- 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4.6 (s, 2), 3 8 (m, 2), 3.4 (m, 2), 3 2 (m, 2), 2.6 (m, 1), 2.4 (m, 1), 2 2 (m, 1), 1.6-1. 3 (m, 4), 0 9 (m, 3) ppm,

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine, NMR (DMSO-d_6) 7 6 (m, 2), 7 3 (m, 4), 6 9 (d, 2), 5 0-4 2 (m, 6), 3 5-3 1 (m, 4), 2 2 (m, 1), 1 2 (d, 3), 0 9 (d, 6) ppm;

(2*S*) -4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-methylpropyl) piperazine,

(2*R*,3*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine, hydrochloride salt, NMR (DMSO-d_6) 7 8 (m, 2), 7.3 (m, 4), 6 9 (d, 2), 5 1- 3 6 (m, 6), 3 2 (m, 4), 1 5-1 2 (m, 6) ppm,

(3*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-butylpiperazine,

(3*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- (1-methylpropyl)piperazine,

(3*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-methylpropyl)piperazine,

(3 *R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- butylpiperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy)methylpiperazine; NMR ($CDCl_3$) 7 3 (m, 8), 6 8 (m,, 5), 4.5 (m, 6), 3 6 (m, 5), 3 0 (m, 1), 2 7 (dd, 1), 2 3 (d, 1), 1 2 (d, 3) ppm;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl) piperazine dihydrochloride salt;

(2*R*)-4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-methylpiperazine hydrochloride salt,

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((4-acetylpiperazin-1-yl)methyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-((trifluoroacetylamino)methyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl)methylpiperazine hydrochloride salt;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine, hydrochloride salt;

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino-4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine; NMR (DMSO-d_6) 9.5 (br s, 1), 8 1 (br s, 1), 7 7 (m, 2), 7 3 (m, 2), 7.0 (m, 2), 5.0 (m, 2), 4.3 (m, 3), 3 8-2 9 (m, 5), 2 1 (s,3), 1 2 (m, 6) ppm;

4-(4-fluorobenzyl)-1-((2-((acetylamino)methyl)-4- chlorophenoxy)methyl)carbonyl-2,5-methylpiperazine, NMR ($CDCl_3$) 7.3 (m, 3), 7 1 (dd, 1), 7.0 (t, 2), 6 7 (d, 1), 4 7 (m, 2), 4 2-3 4 (m, 10), 3 0 (br s, 1), 2 7 (dd, 1), 2 5 (q, 4), 2 2 (d, 1), 2 0 (m, 4), 1 3 (m, 3), 0 9 (m, 3) ppm;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(((*t*-butoxycarbonyl)amino)methylpiperazine,

1-((4-chloro-2- (acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine, NMR (DMSO-d_6) 10.9 (d, 1), 9 5 (s, 1), 8 1 (s, 1), 7 6 (d, 2), 7 3 (t, 2), 7 0 (m, 2), 5.0 (q, 2), 4.7 (m, 1), 4.3 (m, 2), 3.9-2. 8 (m, 6), 2 1 (s, 3), 1 4 (d, 1 5), 1 3 (d, 1 5) ppm,

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 9 5 (d, 1), 8 2 (s, 1), 7 8 (t, 2), 7 3 (t, 2), 7 0 (dt, 2), 6.8 (dq, 1), 6 4 (d, 1), 5 2-4 3 (m, 5), 3 9-2.8 (m, 5), 1 8 (d, 3), 1.3 (m, 6) ppm,

(*trans*)-1-((4-chloro-2-(*iso*- propylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.5 (d, 1), 8 2 (s, 1), 7.8 (t, 2), 7 3 (t, 2), 7 0 (m, 2), 5.2-4.3 (m, 5), 3 9-2 7 (m, 6) , 1 4-1 1 (m, 12) ppm;

(*trans*)-1-((4-chloro-2- (methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 9 3 (s, 1), 8. 2 (s, 1), 7 8 (t, 2), 7.3 (t, 2), 7 1 (m, 2), 5 3-4 2 (m, 5), 4.0 (s, 2), 3 9-2 8 (m, 8), 1.4-1 2 (m, 6) ppm,

(*trans*)-1-((4-chloro- 2-(2-(methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 9 5 (s 1), 8 1 (s, 1), 7.8 (t, 2), 7.3 (t, 2), 7.0 (m, 2), 5.2-4 2 (m, 5) , 3 8 (q, 1), 3.7-3 2 (m, 5), 2.9-2 6 (m, 6), 1 4-1 2 (m, 6) ppm,

(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 9 6 (s. 1), 8 1 (s, 1), 7 8 (t, 2), 7.3 (t, 2), 7 0 (m, 2), 5 2-4.2 (m, 5), 4 0 (q, 2), 3 8 (q, 1), 3.6-3.2 (m, 3), 2 8- 2 6 (m, 5), 1 4-1 2 (m, 9) ppm,

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine, NMR (DMSO-d_6) 10.9 (d, 1), 9 3 (s 1), 7 7 (d, 2), 7 3-7 2 (m, 4), 7.0 (d, 1), 5.0 (m, 2), 4.7 (m, 1), 4 4 (m, 3), 3 9 (m, 1), 3 6 (m, 1), 3 4-2 8 (m, 6), 1.4 (d, 1 5), 1 2 (d, 1 5) ppm,

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 10 0 (s 1), 8 4 (s, 1), 7 3 (m, 2), 7 0 (m, 3), 6 9 (m, 1), 4.7 (m, 3), 4 0 (s, 2), 3 8-3.1 (m, 5), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (br d, 3), 1 0 (br s, 3) ppm;

(*trans*)-1-((4-chloro-2- (ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 9 4 (s, 1), 8 5 (s, 1), 7 3 (m, 2), 7 0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 3 5 (m, 3), 3 1 (m, 2) , 2 7 (dd, 1), 2 5 (q, 1), 2.2 (d, 1), 1 3 (m, 6), 10 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(acetylaminomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 8 0 (br s, 1), 7.3 (m, 3), 7.1 (dd, 1), 7 0 (m, 2), 6. 8 (br d, 1), 4 7 (m, 3), 4.4 (d, 1), 3 8-3 0 (m, 6), 2 7 (m, 1), 2 2 (m, 1), 2 0 (s, 3), 1 3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-(1-(methylsulfonyl)(methyl)aminoethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 8 (m, 1), 5.6 (q, 1), 4.7 (m, 3), 4.2 (m, 1), 3 7 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3 1 (m, 1), 2.8 (d, 3), 2.7 (d, 3), 2 3 (br d, 1), 1.6 (d, 3), 1.3 (m, 3), 0 9 (m, 3) ppm,

(*trans*) -1-((4-chloro-2-(1-(phenylsulfonyl)(methyl)aminoethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 6 (d, 2), 7 3 (m, 6), 6 9 (t, 2), 6 8 (t, 1), 5 6 (q, 1), 4 6 (m, 3), 4 2 (m, 1), 3.6 (m, 2), 3 4 (d, 1), 3 0 (m, 1), 2.6 (m, 4), 2. 4 (s, 3), 2 3 (m, 1), 1 3 (m, 6), 0.9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl)aminoethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 2 (m, 4), 7 0 (t, 2), 6 8 (m, 1), 6 0 (m, 1), 5 4 (q, 1), 4 6 (m, 3), 4 2 (m, 1), 3 5 (q, 2), 3 2 (m, 1), 3,0 (m, 1), 2 6 (m, 4), 2. 2 (m, 3), 1 3 (m, 6), 0 9 (m, 3) ppm;

(*trans*)-1-(2- (4-chlorophenyl)-3-(methylsulfonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (t, 4), 7 2 (br d, 2), 7 0 (t, 2), 5 0 (br s, 1), 4 6 (br s, 1), 4 0 (m, 1), 3 4 (m, 5), 3 0 (m, 2), 2 8 (s, 3), 2 6 (m, 2), 2.2 (br d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 2 (br d, 2), 7.0 (t, 2), 5.2 (m, 1), 4 6 (br s, 1), 4 2 (m, 1), 3 8 (m, 1), 3 4 (m, 5), 3 0 (m, 1), 2 8 (s, 3), 2 6 (m, 2), 2.2 (m, 1), 1 2 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2- (methylsulfonylamino) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 5), 7 0 (t, 2), 6.6 (m, 1), 4 9 (q, 1), 4.6 (m, 0 5), 4 2 (br d, 0.5), 3.8 (m, 1), 3.5 (m, 1), 3 4 (m, 1), 3.0 (m, 2), 2. 7 (m, 6), 2.2 (m, 1), 1.2 (m, 3), 0 8 (m, 3) ppm,

(*trans*)- 1-(2-(4-chlorophenyl)-2-(acetylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.8 (m, 1), 7 3 (m, 5), 7.0 (t, 2), 5 3 (m, 1), 4.6 (m, 0.5), 4 1 (t, 0.5), 3 5 (m, 1), 3 4 (m, 1), 3 0 (m, 3), 2 6 (m, 2), 2 2 (m, 1), 2 0 (m, 4), 1 2 (m, 3), 0 8 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((4-(2,5- di(trifluoromethyl)phenylcarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-

fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 0 (m, 1), 8 1 (m, 2), 7 9 (t, 1), 7.7. (m, 1), 7 4 (d, 1), 7.3 (m, 2), 7.2 (m, 1), 5.4 (m, 1), 5.0 (m, 2), 4 4 (m, 6), 3.4 (m, 9) , 3 0 (m, 1), 2.8 (m, 1), 1.4 (m, 3), 1 2 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((4-(benzylcarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11 0 (m, 1), 7.9 (t, 2), 7 7. (t, 1), 7.6, (s, 1), 7 5 (d, 1), 7 3 (m, 4), 7.2 (m, 3), 5.4 (m, 1), 5 0 (m, 2), 4.4 (m, 6) , 3 7 (m, 2), 3 4 (m, 6), 3.0 (m, 2), 2.8 (m, 1), 1 4 (dd, 3), 1.2 (dd, 3) ppm,

(*trans*)-1-((4-chloro-2-((4-((2,3,4- trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine. NMR (DMSO-d_6) 11 0 (m, 1), 9 0 (s, 1), 7,9 (t, 2), 7 7 (m, 1), 7 6 (s, 1), 7 5 (m, 1), 7 2 (m, 4), 5 4 (m, 1), 5.0 (m, 2), 4.4 (m, 6), 3 4 (m, 8) , 3.1 (m, 2), 2.8 (m, 1), 1.4 (m, 3), 1.2 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 11.0 (m, 1), 8 6 (s, 1), 7 9 (t, 2), 7 7 (m, 1), 7 6 (s, 1), 7 4 (d, 1), 7 3 (m, 1), 7 3 (t, 2), 7 2 (m, 3), 5.4 (m, 1), 5.0 (m, 2), 4.3 (m, 6), 3 4 (m, 9), 3 1 (m, 2), 2.8 (m, 1), 1 4 (dd, 3), 1.2 (dd, 3) ppm;

(*trans*)-1-((4- chloro-2-((*N'*-(2,6-difluorophenyl)ureido)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9 6 (br s, 1), 8.6 (s, 1), 7 4 (quin, 1), 7.3 (t, 2), 7.0 (m, 5), 6 9 (d, 1), 4 7 (m, 3), 4 1 (brs, 0 5), 3 8 (br s, 0 5), 3 5 (q, 2), 3 2 (m, 1), 3 0 (m, 1), 2 6 (dd, 1), 2 2 (d, 1), 1 2 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(ethenylcarbonylamino) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 8 (d, 1), 8 6 (s, 1), 7 3 (m, 3), 7.0 (t, 3), 6 9 (d, 1), 6 4 (dd, 2), 5 8 (dd, 1), 4 7 (m, 3), 3 6 (m, 1), 3 5 (q, 2), 3.2 (m, 1), 3 0 (m, 1), 2 7 (dd, 1), 2 2 (dd, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(cyclopropylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 7 (br s, 1), 8.4 (s, 1), 7 3 (m, 2), 7 0 (m, 3), 6 8 (d, 1), 4 7 (m, 3), 3 7 (m, 1), 3 5 (q, 2), 3 1 (m, 2), 2.7 (dd, 1), 2 2 (dd, 1), 1 7 (m, 1), 1 3 (m, 3), 1 0 (m, 5), 0.8 (m, 2) ppm,

(*trans*)-1-((4-chloro-2-(cyclopentylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 3 (br s, 1), 8.5 (s, 1), 7 3 (t, 2), 7 0 (m, 3), 6 8 (d, 1), 4 7 (m, 3), 3 7 (m, 1), 3 5 (q, 2), 3.1 (m, 2),

2 8 (quin, 1), 2 7 (dd, 1), 2 2 (dd, 1), 1 9 (m, 3), 1.8 (m, 1), 1 6 (m, 3), 1.3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((furan-2-yl) carbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 10.4 (br s, 1), 9 7 (br d, 1), 8 2 (br s, 1), 7.9 (s, 1), 7.7 (m, 2), 7 3 (m, 3), 7 2 (s, 2), 6 7 (d, 1), 5 3 (br d, 1), 5.0 (m, 2), 4 7 (m, 0.5), 4.5 (m, 0.5), 4.2 (m, 3), 3 6 (m, 1) , 3 4 (m, 1), 2.8 (m, 1), 1 3 (m, 3), 1 2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 10 0 (s, 1), 8 6 (s, 1), 8 1 (d, 2), 7 5 (m, 3), 7 3 (t, 2), 7.0 (t, 3), 6 8 (d, 1), 4 7 (m, 3), 37 (m, 1), 35 (q, 2), 3 1 (m, 2), 2 7 (dd, 1), 2 2 (dd, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-2-((ethoxycarbonylmethylcarbonylamino) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 8.6 (m, 1), 7 2 (s, 6), 7.0 (t, 2), 5.4 (m, 1), 4.2 (q, 2), 3 8 (m, 1), 3 5 (m, 1), 3.4 (m, 3), 3.0 (m, 3), 2.6 (m, 2), 2 2 (m, 2), 1 3 (m, 4.5), 1.1 (m, 1 5), 0 9 (dd, 1 5), 0 7 (dd, 1 5) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-2-(*N'*-iso-propylureido) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 6), 7 0 (t, 2), 5 2 (t, 1), 4 6 (m, 0 5), 4 4 (m, 1), 4 2 (t, 0.5), 3 8 (m, 1), 3 5 (m, 1), 3 4 (m, 1), 3.0 (m, 3), 2 6 (m, 1), 2 2 (m, 1), 1 1 (m, 9), 0 9 (dd, 1 5), 0.8 (dd, 1.5) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2-(*N'*-(2-chloroethyl) ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 6), 7 0 (t, 2), 5 2 (t, 2), 4 6 (m, 0 5), 4.2 (t, 0.5), 3.5 (m, 6), 3 0 (m, 4), 2.6 (m, 1), 2.2 (m,1), 1.1 (m, 3), 0. 9 (dd, 1 5), 0 8 (dd, 1.5) ppm;

(*trans*)-1-(2-(4- chlorophenyl)-2- ((2-nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine, NMR ($CDCl_3$) 8.1 (d, 1), 7 7 (q, 1), 7.6 (t, 2), 7.3 (m, 6), 7.0 (t, 2), 5 6 (m, 1), 4 6 (m, 0.5), 4 1 (t, 0 5), 3 7-3 2 (m, 3), 3.0 (m, 4), 2 6 (m, 1), 2.2 (m, 1), 1.2 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 8), 7.0 (t, 2), 6.9 (d, 2), 5 3 (m, 1), 4.6 (m, 0 5), 4.1 (t, 0 5), 3 8 (s, 3), 3. 5 (m, 3), 3 4-2 8 (m, 6), 2.6 (m, 1), 2 2 (m, 1), 1 2 (m, 3), 0.8 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-2-((2,4-dinitrophenyl) sulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 8 6 (s, 1), 8 2 (d, 1), 7 8 (m, 1), 7 3 (m, 4), 7 0 (t, 2), 6 9 (t, 2), 5 0 (m, 1), 4 6 (m, 0 5), 4 1 (m,

0 5), 3 5 (m, 1), 3 4 (m, 1), 3 0 (m, 5), 2 6 (m, 1), 2 2 (m, 1), 1 1 (m, 3), 0 8 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-2- (cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 7 3 (m, 6), 7.0 (t, 2), 5 2 (m, 1), 4 6 (m, 0.5), 4 2 (m, 0.5), 3 5 (m, 2), 3.4 (m, 1), 3 0 (m, 3), 26 (m, 2), 2.2 (m, 1), 1 5 (m, 1), 1 2 (m, 3), 0 9 (m, 3 5), 0.7 (m, 3.5) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-2-((2-cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 6), 7 0 (t, 2), 5 4 (m, 1), 4 6 (m 0 5), 4 2 (m, 0 5), 3.6 (m, 2), 3.4 (m, 1), 3. 0 (m, 4), 2.6 (m, 1), 2 2 (m, 2), 1 6 (m, 10), 1.2 (m, 3), 1 1 (m, 2), 0. 8 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-3-((2- methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,, NMR ($CDCl_3$) 7 3 (d, 4), 7 2 (d, 2), 7 0 (t, 2), 6 0 (br s, 1), 4.6 (m, 0.5), 4 2 (m, 0.5), 3.6 (m, 2), 3 4 (m, 3), 3 0 (m, 2), 2.6 (m, 3), 2 2 (d, 1), 2.0 (m, 4), 1 2 (m, 3), 0.9 (m, 9) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (d, 4), 7 2 (d, 2), 7 0 (t, 2), 6 0 (br s, 1), 4 6 (m, 0 5), 4 2 (m, 0 5), 3 6 (m, 2), 3 4 (m, 3), 3.0 (m, 2), 2 6 (m, 3), 2 4 (m, 1), 2 2 (d, 1), 1 6 (m, 8), 1.1. (m, 4), 0 9 (m, 4) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(*t*- butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (d, 4), 7 2 (d, 2), 7 0 (t, 2), 4.6 (m, 1 5), 4 2 (m, 0.5), 3.6 (m, 2), 3.4 (m, 4), 3 2 (m, 1), 3 0 (m, 1), 2 6 (m, 2), 2.2 (d, 1), 1.3 (s, 9), 1 2 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(ethyl)ureido)propyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (d, 4), 7.2 (d, 2), 7 0 (t, 2), 5 1 (m, 1), 4.9 (m, 1), 4.6 (m, 0 5), 4 2 (m, 0 5), 3.6 (m, 2), 3 4 (m, 4), 3 2 (m, 3), 3 0 (m, 1) , 2.6 (m, 3), 2 2 (m, 1), 1 1 (m, 6), 0 9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl)ureido) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (d, 4), 7 2 (d, 2), 7 0 (t, 2), 5.6 (br s, 1), 5 9 (s, 1), 4 6 (m, 0.5), 4.2 (m, 0 5), 3 6 (m, 5), 3 4 (m, 5), 3.2 (m, 1), 3. 0 (m, 1), 2 6 (m, 3), 2 2 (d, 1), 2 0 (t, 2), 1 2 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (d, 4), 7 2 (d,

2), 7 0 (t, 2), 5 8 (br d, 1), 4.6 (m, 0.5), 4 2 (m, 0 5), 3.6 (m, 6), 3.4 (m, 4), 3 3 (t, 4), 3 0 (m, 2) , 2 6 (m, 3), 2 2 (m, 1), 1.2 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((*N'*-(methoxycarbonylmethylcarbonyl)- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9.6 (br s, 1), 8. 4 (d, 1), 7 3 (dd, 2), 7 0 (t, 3), 6 8 (d, 1), 4 7 (m, 3), 4 3 (s, 2), 3 8 (s, 3), 3 6 (m, 4), 3 5 (m, 2), 3 1 (m, 4), 2 7 (dd, 1), 2.2 (d, 1), 1. 3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(2-methoxycarbonylethyl)carbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9.6 (br s, 1), 8 4 (d, 1), 7.3 (dd, 2), 7 0 (t, 3), 6 8 (d, 1), 4 7 (m, 3), 4 3 (s, 3), 3 8 (s, 3), 3.6 (q, 2), 3 2 (s, 3), 3.1 (s, 2) , 2 7 (m, 5), 2 2 (d, 1), 1.3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl) aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 6 (br s, 1), 8.4 (d, 1), 7 3 (dd, 2), 7 2 (t, 1), 7 0 (m, 6), 6 8 (d, 1), 5. 4 (t, 1), 4 6 (m, 3), 4.4 (d, 2), 4 3 (s, 2), 3 8 (m, 1), 3 5 (q, 2), 3 1 (m, 5), 2 6 (m, 1), 2 3 (s, 3), 2.2 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((*N'*-(3- trifluoromethyl-4- fluorophenyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 8 (br s, 1), 8 4 (d, 1), 8.1 (br s, 1), 7 6 (m, 2), 7 3 (dd, 2), 7 0 (m, 4), 6 8 (d, 1), 4 7 (m, 3), 4.3 (t, 2), 3 7 (m, 1), 3 6 (q, 2), 3 2 (s, 3), 3 1 (m, 2), 2.7 (m, 1), 2.2 (d, 1), 1.3 (m, 3), 0. 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((*N'*-(4- methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 6 (br s, 1), 8 4 (d, 1), 7 3 (m, 2), 7.2 (d, 2), 7 1 (d, 2), 7 0 (m, 3), 6 8 (d, 1), 5 4 (t, 1), 4 7 (m, 3),4 4 (d, 2), 4 2 (d, 2), 3 8 (m, 1), 3.6 (q, 2), 3.1 (m, 5), 2 7 (m, 1), 2 3 (s, 3), 2.2 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2- ((*N'*-(3-chlorophenyl)carbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 9 (br s, 1), 8.4 (d, 1), 7.5 (s, 1), 7 3 (m, 5), 7 0 (t, 3), 6.8 (d, 1), 4 7 (m, 3), 4 4 (br s, 2), 4 1 (m, 1), 3 6 (m, 1), 3 5 (q, 2), 3 2 (m, 3), 3.0 (m, 1), 2 7 (dd, 1), 2 2 (d, 1), 1 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'* -(4-fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 7 (br s, 1), 8.4 (s, 1), 7.3 (m, 4), 7 0 (m, 5), 6.8 (d, 1), 5 5 (t, 1), 4 7 (m, 2) 4 4 (d, 2), 4 2 (m, 2), 3 6 (m, 1), 3 5 (q, 2), 3 1 (m, 5), 2 7 (m, 1), 2.2 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(*N'*-(methoxymethylcarbonyl) glycinamido)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 10 1 (br s, 1), 8.4 (d, 1), 7 3 (t, 3), 7 0 (t, 3), 6 8 (d, 1), 4.7 (m, 3), 4 2 (d, 2), 4.0 (s, 2), 3 6 (m, 1), 3 5 (q, 2), 3.4 (s, 3), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonylaminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 9 (br s, 1), 8 4 (m, 2), 7.3 (m, 3), 7 0 (m, 3), 6 8 (d, 1), 4 7 (m, 3), 4 4 (m, 6), 3 6 (m, 1), 3.5 (q, 2), 3 1 (m, 2), 2.7 (dd, 1), 2 2 (d, 1), 1 3 (m, 6), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 10 4 (br s, 1), 8 4 (d, 1), 7 9 (d, 1), 7 5 (d, 1), 7.4 (t, 1), 7 3 (m, 2), 7 1 (t, 1), 7.0 (t, 3), 6 8 (m, 2), 4 7 (m, 3), 4 4 (d, 2), 3 6 (m, 1), 3.5 (q, 2), 3 1 (m, 2), 2 7 (dd, 1), 2 2 (d, 1), 1 3 (m, 3), 0.9 (m, 3) ppm,

(*trans*)-1-((4- chloro-2-(*N'*-(2,3-difluorophenylcarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 10 3 (br s, 1), 8 4 (d, 1), 7 8 (t, 1), 7.5 (quin, 1), 7 3 (m, 3), 7 2 (m, 1), 7 0 (t, 3), 6.8 (d, 1), 4 7 (m, 3), 4 4 (d, 2), 36 (m, 1), 3.5 (q, 2), 3 1 (m, 2), 2 7 (dd, 1), 2 2 (d, 1), 1.3 (m, 3), 0. 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9 9 (br s, 1), 8 3 (br s, 1), 7 3 (m, 6), 7.0 (t, 6), 6 8 (m, 3), 6 5 (m, 1) , 4 7 (m, 3), 4 4 (m, 2), 3 6 (m, 1), 3 5 (q, 2), 3.1 (m, 2), 2 7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4- chloro-2-(*N'*-(2,4-difluorophenylcarbonyl)glycinamido)phenoxy)methyl) -carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 10 3 (br s, 1), 8 4 (d, 1), 8 1 (q, 1), 7 5 (m, 1), 7 3 (m, 2), 7.0 (t, 3), 6 8 (m, 3), 4 7 (m, 3), 4 4 (d, 2), 3.6 (m, 1), 3 5 (q, 2), 3 1 (m, 2), 2 7 (dd, 1), 2 2 (d, 1), 1.3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8 0 (m, 1), 7 8 (d, 1), 7 3 (m, 5), 7.2 (dd, 1), 7.0 (m, 3), 6.8 (d, 1), 4 8 (m, 3), 4.6 (d, 2), 4 4 (m, 0.5), 3.9 (m, 0 5), 3 5 (q, 2) , 3.1 (m, 2), 2.6 (m, 1), 2 2 (m, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2- ((ethoxycarbonylmethylcarbonyl)aminomethyl)phenoxy)-methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8 4 (br s, 1), 7.3 (m, 3), 7 2 (dd, 1), 7.0 (m, 2), 6.8 (d, 1), 4 8 (m, 3), 4 5 (d, 2), 4.2 (m, 3), 3 6 (m, 1), 3.5 (q, 2), 3 3 (s, 2), 3 1 (m, 1), 2 6 (m, 1), 2 2 (d, 1), 1 3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)- 1-((4-chloro-2-(*N'*-(3-chloropropyl)ureidomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7 2 (dd, 1), 7 0 (m, 2), 6 8 (d, 1), 4.8 (m, 4), 4.4 (d, 2), 4.2 (m, 1), 3.6 (m, 5), 3 3 (m, 3), 3 1 (m, 1), 2 6 (m, 1), 2. 2 (d, 1), 1 9 (quin, 2), 1.3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 8 2 (m, 1), 7.3 (m, 6), 7 2 (dd, 1), 7 0 (t, 2), 6 8 (d, 1), 4,8 (m, 3), 4.4 (d, 2), 3 8 (m, 1), 3 5 (q, 2), 3 2 (m, 1), 3 1 (m, 1), 2 6 (m, 1), 2 2 (m, 1), 1 3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((3-fluorophenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 8 6 (m, 1), 7.8 (t, 2), 7.3 (m, 4), 7 2 (dd, 1), 7.1 (dt, 1), 7.0 (t, 2), 6 8 (d, 1), 4 8 (m, 3), 4 6 (d, 2), 3 8 (m, 1), 3 5 (q, 2), 31 (m, 2), 2 6 (m, 1), 2.2 (d, 1), 1. 3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2- (*N'*-(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 3), 7 2 (dd, 1), 7 0 (t, 2), 6 9 (m, 1), 6.8 (d, 1), 5 1 (m, 1), 4.8 (m, 3), 4 4 (d, 2), 4.1 (q, 2), 3 6 (m, 2), 3 4 (m, 3), 3.2 (m, 1), 3 1 (m, 2), 2 7 (m, 1), 2 5 (t, 2), 2 2 (d, 1), 1 3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 8.9 (m, 1), 7 8 (m, 2), 7 2 (s, 1), 7.3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6 8 (d, 1), 4.8 (m, 3), 4.6 (d, 2), 4.4 (m, 0 5), 3 9 (m, 0 5), 3 5 (q, 2), 3 1 (m, 2), 2 6 (m, 1), 2 2 (m, 1), 1 3 (m, 3), 0 9 (m, 3) ppm, and

(*trans*)-1-((4-chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 8), 7.0 (m, 3), 6.8 (d, 1), 4 9 (s, 1) , 4 6 (d, 2), 4.4 (m, 2), 3 8 (m, 1), 3 5 (q, 2), 3.2 (m, 1), 3.0 (m, 1), 2.7 (m, 2), 2 2 (m, 1), 2 0 (m, 1), 1 3 (m, 5), 0 9 (m, 3) ppm

C In a similar manner, the following compounds of formula (Ib) were made.

1-(2-(4-chlorophenyl)ethenyl) carbonyl-4-(4-fluorobenzyl)piperazine,

1-(2-(4-chlorophenyl) ethyl)carbonyl-4-(4-fluorobenzyl)piperazine,

1-(1-(*t*- butoxycarbonyl)amino-2-(4-chlorophenyl)ethyl)carbonyl-4-(benzyl) piperazine,

1-(3-(*t*-butoxycarbonyl)amino-2-(4- chlorophenyl)propyl)carbonyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 2 (m, 8), 4.8 (m, 1), 3 6-3 3 (m, 8), 2 6 (m, 2), 2 3 (m, 3), 2.1 (m, 1), 1 4 (s, 9) ppm,

1-(2-(3,4,5- trimethoxyphenyl)ethenyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 6 (d, 1), 7 3 (m, 4), 6.7 (m, 3), 3.9-3.6 (m, 13), 3 5 (s, 2), 2 5 (m, 4) ppm,

1-(1-(3,4-dimethoxyphenyl)- 2-(4-chlorophenyl)ethenyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-(2-(3,4,5-trimethoxyphenyl)ethyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-(((acetyl)amino)(4-chlorophenyl)methyl)carbonyl-4-(4- fluorobenzyl)piperazine, hydrochloride salt

EXAMPLE 2

Compounds of Formula (Ia)

A *To a solution of (2R,5S)-1-(chloro)acetyl-4-(4-fluorobenzyl)-2, 5-dimethylpiperazine* (0 29 g, 1 mmol) in anhydrous DMF (5 mL) was added 4- hydroxy-3-methoxyphenylacetonitrile (0.20 g, 1 2 mmol) and potassium carbonate (0 28 g, 2 mmol, powdered) The resultant mixture was stirred at 50°C. After 15 hours analysis by analytical HPLC (HPLC on a C18 Vydac column with 20-70% acetonitrile in water gradient with 0 1% trifluoroacetic acid) showed complete consumption of starting material had occurred The mixture was poured into water and extracted with three portions of ethyl acetate. The combined organic extracts were washed sequentially with 0 5 N aqueous KOH solution, water, then brine. It was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil This was dissolved in ethyl acetate and treated with a solution of HCl in anhydrous ether Filtration of the resultant solid afforded 0 38 g (85% yield) of

(2*R*,5*S*)-1- ((4-(cyano)methyl-2-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)-2,5- dimethylpiperazine, hydrochloric acid salt as a white solid· NMR (DMSO- d_6) 11.5 (br s, 1), 7.6 (m, 4), 6.9 (m, 3), 4.8 (br s, 2), 4 4 (br s, 3), 4 0 (m, 1), 3 9 (s, 2), 3 8 (s, 3), 3 6 (m, 1), 3 3 (m, 2), 3 2-2.9 (m, 3) ppm.

B In a similar manner, other compounds of formula (Ia) were made·

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10 4 (br d, 1), 7.7 (m, 2), 7.2 (m, 4), 6.9 (br s, 1), 5 0 (m, 1), 4.8 (m, 2), 4.3 (m, 3) , 3 7 (m, 2), 3.3 (m, 2), 2 9 (m, 1), 1 4-1 2 (m, 6) ppm,

1-((2- acetylaminophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10 6 (br s, 1), 9 4 (s, 1), 8 0 (d, 1), 7.8 (br s, 2) , 7 2 (t, 2), 6 9 (m, 3), 5 0 (m, 3), 4 3 (m, 3), 3.8 (q, 1), 3. 6 (br s, 1), 3 4 (m, 1), 2 8 (m, 1), 2 1 (s, 3), 1 3 (dd, 3), 1 2 (d, 3) ppm;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2- (methoxycarbonyl)methyl-4-(4-fluorobenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-2-(ethoxycarbonyl)-4-(4-fluorabenzyl) piperazine,

(*cis*)-1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6 2 (s, 2), 4 7-4 2 (m, 4), 3 8 (m, 9), 3 5 (s, 2), 2 6 (d, 2), 2 2 (dd, 2), 1 3 (m, 6) ppm,

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 2), 7.0 (t, 2), 6 2 (s, 2), 4 6 (s, 3), 4 4 (m, 1), 4 1 (m, 1), 3 8 (s, 6), 3 85 (s, 3), 3 5 (m, 2), 2.8 (d, 1), 2 6 (d, 1), 2 1 (m, 2), 1 3 (m, 3) ppm,

1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6.9 (d, 2), 4 6 (s, 2), 4 4 (m, 1), 4 1 (m, 1), 3 7 (m, 1), 3.4 (m, 2), 2 8 (m, 1), 2 6 (d, 1), 2 0 (m, 2), 1.3 (m, 3) ppm;

1-((4- chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4 6 (s, 2) , 4 0 (m, 2), 3.7 (m, 1), 3 4-2 9 (m, 3), 2 7 (m, 1), 2 5 (m, 1), 2 1 (m, 1) , 1.1 (m, 3) ppm;

(2*S*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4.6 (s, 2), 4 4 (m, 1), 4.1 (m, 1), 3 7 (m, 1), 3.4 (m, 2), 2.8 (m, 1), 2 6 (d, 1), 2 0 (m, 2), 1 3 (m, 3) ppm,

4-((4-chlorophenoxy)methyl) carbonyl-3-(((4-chlorophenyl)amino)carbonyl)methyl-1-(benzyl)piperazin-2- one,

1-((phenoxy)methyl)carbonyl-2-ethyl-4-(4-fluorobenzyl) piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-2-hydroxymethyl- 4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6.9 (d, 2), 4 7-4 5 (m, 3), 4.2-3.3 (m, 5), 3 2-2 7 (m, 2), 2 3- 2 0 (m, 4) ppm;

1-(1-(4-chlorophenoxy)-1-methylethyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine,

(2*S*,5*R*)-1- ((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 2), 7.0 (t, 2), 6 2 (s, 2), 4 6 (m, 34), 4 2 (m, 1), 3 8 (m, 6), 3.5 (m, 3), 3.0 (m, 1), 2 7 (dd, 1), 2 2 (d, 1), 1 3 (m, 4), 0.9 (m, 3) ppm,

(2*R*,5*S*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6 2 (s, 2), 4 6 (m, 3), 4 2 (m, 1), 3 8 (m, 6), 3. 5 (m, 3), 3 0 (m, 1), 2 7 (dd, 1), 2 2 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7 0 (t, 2), 6 3 (s, 2), 4 7 (m, 2), 4 2 (m, 1), 3 8 (s, 6), 3.5 (m, 4), 3 0 (m, 1), 2 7 (dd, 1), 2 2 (d, 1), 1.3 (m, 3), 0 9 (m, 3) ppm,

(2*S*,5*R*)-1-((4-bromo-3,5-dimethoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 10 7 (d, 1), 7.8 (m, 2), 7 3 (m, 2), 6.3 (s, 2), 4.9 (m, 2), 4 3 (m, 2), 4 0-2 8 (m, 12), 1 4-1 2 (m, 6) ppm,

(2*S*,5*R*)-1-((4-nitro-3-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 10.4 (s, 1), 8.2 (d, 1), 7 3 (m, 4), 7 0 (t, 2), 4 8 (m, 3), 4 2-2 3 (m, 7), 1 3 (m 3), 1 0 (m, 3) ppm;

(*trans*) -1-((4-chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 9 2 (br s, 1), 8 2 (s, 1), 7 4 (m, 3), 7.0 (t, 2), 6 8 (d, 1), 5 9 (s, 1), 5 0-4.0 (m, 3), 3 8-3 0 (m, 5), 2.8 (d, 1), 2 3 (d, 1), 1 3 (m, 3), 1 0 (br s, 3) ppm;

(2*R*,5*S*)-1-((4-chloro-2-(aminocarbonyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 2 (br s, 1), 8 2 (s, 1), 7 4 (m, 4), 7 0 (t, 2), 6 8 (d, 1), 5.8 (s, 1), 4 7 (m, 2), 3 7-3.1 (m, 5), 2 8 (d, 1), 2 3 (d, 1), 1 3 (d, 3), 1 0 (br s, 3) ppm,

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-((amino)carbonyloxy)methyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 11 (br d, 1), 7 9 (br s, 1), 7 6 (m, 2), 7 3 (m, 4), 5.2 (d, 1), 5.0 (m, 2), 4 3 (m, 4), 4. 0 (m, 1), 3 6 (m, 2), 1 3 (m, 6) ppm;

(*trans*)-1-((4- chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 10 9 (br d, 1), 7 9 (br s, 2), 7 6 (m, 1), 7 3 (m, 4), 5 0 (m, 2), 4 5 (s, 2), 4.3 (m, 2), 3 7-3.3 (m, 6), 1.3 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt; NMR (DMSO-d_6) 7 7 (br s, 3), 7.3 (m, 5), 5.2 (d, 1), 5 0 (m, 2), 47-4 2 (m, 4), 3 9-3 4 (m, 3), 1 3 (m, 6) ppm,

(*trans*)-1-((2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 9.1 (br s, 1), 8 2 (d, 1), 7 4 (dd, 1), 7. 3 (br s, 2), 7.1 (t, 1), 7 0 (m, 2), 6 9 (d, 1), 5.8 (br s, 1), 4.7 (m, 2) , 4.2 (m, 1), 3 7-3 4 (m, 3), 3.0 (br s, 1), 2 7 (br s, 1), 2 3 (d, 1), 1 3 (m, 3), 1.0 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-amino-5- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt, NMR ($CDCl_3$) 10 9 (br d, 1), 7 8 (m, 2), 7 5 (dd, 1), 7.3 (m, 2), 6 8 (s, 1), 5 0 (m, 3), 4 3-3.2 (m, 7), 1.4-1 2 (m, 6) ppm,

(*trans*)-1-((4-methyl-2-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 10.9 (br d, 1), 10 4 (s, 1), 7.9 (s, 2), 7.5 (m, 2), 7.3 (m, 2), 7 0 (d, 1), 5 2 (m, 1), 5 0 (m, 2), 4 6 (m, 1), 4.3 (m, 3), 3.6 (m, 2), 2.8 (m, 1), 2.5 (s, 3), 1 4-1 1 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 10.9 (br d, 1), 10 4 (s, 1), 7 8 (s, 1), 7 5 (dd, 1), 7 3 (dd, 2), 7 0 (m, 3), 4.8 (m, 3), 4.1 (m, 1), 3 5 (m, 3), 3 0 (br s, 1), 2 7 (dd, 1), 2 5 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine hydrochloride salt; NMR (DMSO-d_6) 11 0 (d, 1), 7 8 (t, 2), 7 3 (t, 2), 7 1 (m, 2), 6 8 (m, 2), 4 9-3 3 (m, 9), 2.8 (t, 1), 2 2 (s, 3) , 1 4-1 1 (m, 6) ppm;

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 11 0 (d, 1), 7 8

(t, 2), 7 3 (m, 3), 7.1 (t, 1), 6.9 (m, 2), 5 0-3 2 (m, 11), 2.8 (t, 1), 1 4- 1.1 (m, 6) ppm;

(*trans*)-1-((3-chloro-5-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 10 8 (d, 1), 7.8 (m, 2), 7.3 (t, 2), 6.6 (s, 2), 6.5 (br s, 1), 5 0-3 2 (m, 12), 2 8 (m, 1), 1 4-1 2 (m, 6) ppm;

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 11 1 (d, 1), 7.9 (m, 2), 7 7 (br s, 1), 7 2 (m, 4), 5 2-3 3 (m, 12), 2 8 (t, 1), 1 4-1 2 (m, 6) ppm,

1- ((phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11 (br d, 1), 7 7 (m, 2), 7 3 (m, 4), 6.9 (m, 3), 4. 9 (m, 3), 4 3 (m, 3), 4 0-2.8 (m, 5), 1 4 (d, 1 5), 1 2 (d, 1 5) ppm;

(*trans*)-1-((4-chlorophenylamino)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7 4 (dd, 2), 7.1 (m, 4), 6 6 (d, 2), 5 8 (t, 1), 4 5 (br s, 0.5), 4.0 (br m, 1 5), 3 8 (br m, 1), 3.8-3.3 (m, 3), 3 0 (m, 2), 2.6 (m, 1), 2 2 (d, 1), 1 1 (br d, 3), 0.9 (br d, 3) ppm,

(*trans*)-1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 (br d, 1), 7 7 (m, 4), 7 3 (m, 3), 5.0 (q, 2), 4 7 (m, 0 5), 4.4 (m 2 5), 3 8 (m, 0.5), 3 6-2 9 (m, 6), 1 4 (d, 1 5), 1 3 (d, 1 5) ppm;

(*trans*)-1-((4-chloro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10.8 (br d, 1), 7 9-6 8 (m, 7), 5 1-2 8 (m, 10), 2.2 (s, 3), 1 3 (m, 6) ppm;

(*trans*)-1-((4-chloro- 2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 7 3 (m, 2), 7 0 (t, 2), 6.8 (m, 3), 4 8 (br s, 3). 4 1 (br s, 1), 3 5 (q, 3), 3 2 (q, 4), 3 0 (br s, 1), 2 7 (dd, 1), 2 2 (d, 1), 1 3 (br s, 3), 1 (m 9) ppm,

(*trans*)-1-((4-chloro-2-hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 2), 7 0-6 7 (m, 5), 4.9 (m, 0 5), 4.6 (br s, 2), 4.2 (m, 0.5), 3.6-3.2 (m, 3), 3 0 (br d, 1), 2 7 (br d, 1), 2 2 (d, 2), 1.3 (m, 3), 0 9 (m, 3) ppm,

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10 8 (d, 1), 7 7 (m, 2), 7.3 (m, 4), 6 9 (d, 1), 5 0-4 3 (m, 6), 3 9-2.9 (m, 7), 1 4 (d, 1 5), 1.2 (d, 1.5) ppm,

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0-6.7 (m, 3), 4 7 (m, 4), 4 1 (m, 1), 3 5 (m, 2 5), 3.2 (m, 0 5), 3 0 (s, 1), 2 7 (dd, 1), 2 2 (d, 1), 2 1 (m, 1), 1 2 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(ureidomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7 4 (m, 2), 7.1 (m, 4), 6.9 (d, 1), 6 4 (t, 1), 5 6 (s, 2), 5.0-4 0 (m, 4) , 3 5 (m, 2), 3.3 (d, 2), 3 0 (m, 2), 2 2 (m, 2), 1.2 (br d , 3), 0 9 (br d, 3) ppm;

1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2-methyl- 4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 2 (br d, 1), 7 7 (m, 2), 7 3 (t, 2), 6 9 (m, 3), 5.0-4.2 (m, 5), 3.9 (m, 1), 3 6 (m, 1), 3 4 (m, 1), 3.0 (m, 3), 1 4 (d, 1 5), 1 3 (d, 1 5) ppm,

1-((4-chloro-3-aminophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 2 (br d, 1), 7 8 (br s, 2), 7 3 (t, 2), 7 0 (d, 1), 6 4 (s, 1), 6 2 (d, 1), 4 8-4 2 (m, 5), 4 0 (m, 1), 3 6 (m, 1), 3 4 (d, 1), 3 2-2 9 (m, 4), 1 3 (m, 3) ppm;

(2*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9 0 (s, 1), 8 2 (s, 1), 7 3 (t, 1), 7 0 (t, 3), 6 8 (q, 3), 5 0 (s, 2), 4 6 (dt, 2), 4.4 (d, 0 5), 3.7 (br s, 0.5), 3 4 (m, 2 5), 3 0 (t, 0 5), 2.8 (m, 1), 2 6 (d, 1), 2.1 (m, 3), 1.4 (d, 1 5), 1 3 (d, 1 5) ppm,

(2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9.0 (s, 1), 8 2 (s, 1), 7 3 (t, 1), 7.0 (t, 3), 6 8 (q, 3), 5.0 (s, 2), 4.6 (dt, 2), 4 4 (d, 0.5), 3.7 (br s, 0 5), 3.4 (m, 2 5), 3 0 (t, 0 5), 2 8 (m, 1), 2.6 (d, 1), 2.1 (m, 3), 1 4 (d, 1 5), 1 3 (d, 1 5) ppm,

(*trans*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10 8 (br s, 1), 8 2 (br s, 2), 7.8 (br s, 2), 7 7 (br s, 1), 7 3 (m, 2), 6.8 (br s , 2), 5 2- 4 3 (m, 5), 3 9-3 1 (m, 5), 2 8 (t, 1), 1 5-1.1 (m, 6) ppm;

(2*R*,5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 0 (s, 1), 8 3 (s, 1), 7.3 (t, 1), 7 0 (t, 3), 6 8 (m, 3), 5 0 (s, 2), 4 6 (m, 2), 4.2 (d, 0 5), 3 7-3 4 (m, 2 5), 3.2 (m, 2), 2.7 (d, 1), 2 5(m, 1), 2.2 (d, 1), 1 3 (br d, 3), 1 0 (br d, 3) ppm;

(*trans*)-1- ((4-bromo-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 10.4 (s, 1), 8.0 (s, 1), 7 6 (dd, 1), 7.3 (m, 2), 7 0 (m, 3), 4.8 (m, 3), 4 1 (br d, 1), 3 5 (m, 3), 3 0 (m, 1), 2 7 (dd, 1), 2 3 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm,

1- ((4-chloro-2-methoxycarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11.0 (br d, 1), 7 7 (m, 3), 7 6 (dd, 1), 7.3 (t, 2), 7.0 (d, 1), 5 0 (do, 2), 4 7 (m, 1), 4 4 (m, 3), 3 8 (m, 4), 3 4 (m, 2), 3 0 (m, 2), 1 4 (d, 1 5), 1.2 (d, 1 5) ppm;

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 9 (br s, 2), 7 8 (s, 1), 7 4 (m, 1), 7 1 (t, 2), 7.0 (d, 1), 4.8 (m, 3), 4 4 (m, 2), 3.9 (m, 4), 3.5 (m, 2), 2.8 (m, 2), 1 6 (m, 3) , 1 3 (m, 3) ppm;

1-((4-chloro-2-aminocarbonylphenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9 6 (br s, 1), 8 0 (s, 1), 7.6 (dd, 1), 7 4 (dd, 2), 7 2 (t, 2), 6.9 (d, 1), 5 0 (m, 3), 4 4 (m, 2), 4 0 (m, 1), 3 8 (m, 2), 3 6 (m, 1), 3 1 (m, 1), 2 9 (m, 1) , 1.6 (d, 1 5), 1 4 (d, 1 5) ppm;

1-((4-chloro-2- (aminocarbonyl) phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11.2 (br s, 1), 7.9 (br s, 1), 7.7 (m, 3), 7 2 (m, 2), 6.6 (d, 1), 4 8 (br s, 1), 4 4-3 9 (m, 6), 3.4 (d, 1), 3 0 (m, 3), 1 4 (m, 3) ppm;

(2*R*)-1-((4-chloro-2- aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 9 1 (s, 1), 8 2 (s, 1), 7.4 (dd, 1), 7.3 (m, 3), 7 0 (t, 2), 6 8 (d, 1), 5 8 (br s, 1), 4 8 (m, 3), 3 5 (m, 3), 2.9 (d, 1), 2 7 (d, 1), 2 2 (m, 2), 1.4 (d, 1 5), 1 3 (d, 1 5) ppm;

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 0 (br d, 1), 10 4 (s, 1), 7 6 (m, 4), 7 3 (t, 2), 7.2 (d, 1), 5 2 (m, 2), 4.7 (m, 1), 4 3 (m, 3), 3 9 (m, 1), 3 6 (m, 1), 3 1 (m, 3), 1 5 (d, 1 5), 1.3 (d, 1 5) ppm,

(2*R*,5*S*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10 5 (s, 1), 7.8 (s, 1), 7 5 (d, 1), 7 3 (m, 2), 7 0 (t, 3), 4 8 (m, 3), 41 (m, 1), 3 5 (m, 3), 3 1 (br s, 1), 2.7 (dd, 1), 2 3 (dd, 1), 1 3 (m, 3), 0 9 (m, 3) ppm;

(2*R*)-1-((4-chloro- 2-formylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 10 4 (s, 1), 7 8 (s, 1), 7 5 (d, 1), 7.3 (m, 2), 7 0 (t, 3), 4 8 (br s, 2), 4.7 (m, 1), 4 2 (m, 1), 3 4 (m, 3), 3. 1 (m, 1) , 2 8 (br d, 1), 2 6 (br d, 1), 2 1 (m, 1), 2 0 (dd, 1), 1.3 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-cyanophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 5 (dd, 1), 7 3 (m, 2), 7 0 (m, 4), 4 8 (m, 3), 4 1 (m, 1), 3 5 (m, 3), 3 0 (m, 1), 2 7 (m, 1), 2 2 (m, 1), 1 3 (m, 3), 0 8 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10 8 (br d, 1), 7 8 (s, 2), 7.5 (m, 2), 7.3 (m, 3), 7 2 (m, 1), 5 3 (m, 1), 5 0 (s, 2), 4 3 (m, 3), 4 0 (m, 1), 3.8-3.3 (m, 2), 2. 8 (m, 1), 2 6 (s, 3), 1.4 (dd, 3), 1.3 (m, 3) ppm,

1-((2- (acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 11.0 (br s, 1), 9.4 (s, 1), 8.0 (d, 1), 7 6 (d, 2), 7 3 (t, 2), 7 0 (m, 3), 4 9 (q, 2), 4 7 (m, 1), 4. 3 (m, 3), 3 9 (m, 1), 3.6-2 8 (m, 4), 2 1 (s, 3), 1 4 (d, 1.5), 1 3 (d, 1 5) ppm,

(*trans*)-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11 0 (br d, 1), 7 9 (s, 2), 7 5-7 3 (m, 6), 5 2 (d, 1), 4 9 (m, 2), 4 3 (m, 3), 3.6 (m, 2) , 3 2 (m, 1), 2 8 (m, 1), 1 5-1 2 (m, 6) ppm,

(2*R*, 5*S*)-1-((3-hydroxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6)10.5 (br d, 1), 9 3 (s, 1), 7.8 (s, 2), 7 2 (m, 2), 6.2 (s, 2), 6 1 (s, 1), 4.7 (m, 4) , 4 3 (m, 3), 3.8 (m, 1), 3 6 (m, 1), 2 8 (m, 1), 2 2 (s, 3), 1.4 (m, 3), 1 2 (m, 3) ppm;

(*trans*)-1-((4-methyl-2-aminophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO- d_6) 11 0 (br m, 1), 7.8 (s, 2), 7 2 (m, 5), 5 3 (m, 1), 5 0 (m, 2), 4 3 (m, 3), 4 0 (m, 1), 3.5 (m, 2), 2 8 (m, 1), 2 2 (s, 3), 1 3 (m, 6) ppm;

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11 0 (br d, 1), 10 0 (s, 1), 7 9 (s, 2), 7 5 (m, 2), 7 3 (m, 3), 6.9 (m, 1), 5. 2 (m, 1), 4 9 (m, 2), 4.3 (m, 3), 4 0 (m, 1), 3.6 (m, 2), 2 8 (m, 1) , 1.3 (m, 6) ppm,

(*trans*)-1-((4-methyl-2-acetylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.5 (s, 1), 7.3(m, 3), 7 0 (t, 2), 6 8 (d, 1), 4 7 (m, 3), 4 2 (br d, 1), 3 6 (m, 1), 3 5 (q, 2), 3.0 (br s, 1), 2 7 (m, 4), 2. 2 (m, 4), 1 3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((2- methoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 12.1 (s, 1), 7 8 (m, 3), 7.3 (br s, 1), 7 0 (br s, 4), 4 8 (m, 2), 4 3 (m, 3), 3.9 (m, 5), 3.6 (m, 1), 2.8 (m, 1), 2 4 (m, 1), 1 6 (m, 3), 1 3 (m, 3) ppm,

(*trans*)-1-((3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR (DMSO-d_6) 10 8 (br d, 1), 7 8 (m, 3), 7 7 (m, 1), 7 6 (t, 1), 7.4 (d, 1), 7 3 (t, 2), 5 2 (m, 1), 5 0 (m, 2), 4 7 (m, 1), 4 3 (m, 3), 4 0 (m, 1), 3 6 (m, 1), 2 8 (m, 1), 1 4 (m, 3), 1 3 (m, 3) ppm,

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO- d_6) 9.7 (br d, 1), 8 6 (s, 1), 8.5 (s, 1), 8 1 (d, 1), 7.8 (s, 1), 7.6 (br s, 3), 7.3 (t, 3), 5.4 (d, 1), 5.1 (m, 2), 4 6 (m, 1), 4 3 (s, 2),4.2 (m, 1), 3.7 (m, 1), 3.4 (m, 1), 3.0 (m, 1), 2 6 (s, 3), 1.4 (m, 3), 1 2 (m, 3) ppm;

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl) carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 2 (br d, 1), 8.0 (m, 3), 7 3 (m, 2), 7.0 (m, 2), 5 3 (d, 1), 5 0 (m, 2) , 4 3 (m, 3), 3.7-3 3 (m, 2), 3 0 (m, 1), 2 8 (m, 1), 2 6 (s, 3), 1.4 (m, 3), 1.3 (m, 3) ppm,

(*trans*)-1-((5-nitro-2-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO- d_6) 10 5 (br d, 1), 7 7 (m, 4), 7 4 (d, 1), 7 3 (t, 2), 5 3 (d, 1), 5 1 (m, 2), 4 7 (m, 1), 4.3 (m, 2), 3 9 (q, 1), 3 6 (br d, 1), 3 4 (m, 1), 2 9 (dd, 1), 2 3 (s, 3), 1 4 (m, 3), 1 3 (m, 3) ppm;

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 2 (br d, 1), 7 9 (t, 2), 7 3 (m, 4), 7 0 (d, 1), 4 8 (m, 3), 4 3 (m, 3), 3.9 (m, 1) , 3 6 (m, 1), 3 2 (m, 1), 2.8 (t, 1), 1 4 (dd, 3), 1 3 (dd, 3) ppm,

(*trans*)-1-((5-nitro-2-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11 2 (br d, 1), 7.9 (t, 2), 7 7 (d, 1), 7.6 (s, 1), 7.3 (t, 2), 6 7 (d, 1) , 5. 0 (m, 3), 4 7 (m, 1), 4 3 (m, 2), 4.0 (q, 1), 3.6 (m, 1), 3 3 (m, 1), 2 8 (t, 1) , 1 4 (dd, 3), 1 3 (dd, 3) ppm,

(*trans*)-1-((2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.3 (m, 1), 7 9 (br s, 2), 7 8 (br m, 1), 7 3 (m, 4), 7 0 (t, 1), 5 3 (m, 1), 5.0 (m, 2), 4 6 (m, 1), 4 3 (m, 2) , 3 6 (m, 3), 2 8 (m, 1), 1.3 (m, 6) ppm,

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10 5 (br d, 1), 7 8 (s, 2), 7.3 (m, 2), 7.1 (t, 1), 6 5 (m, 3), 4 8 (m, 2), 4.3 (m, 3), 3 8 (m, 1), 3 6 (m, 1), 3. 4 (m, 2), 2.8 (t, 1), 1 4 (m, 3), 1 2 (m, 3) ppm;

(*trans*)- 1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,, NMR (DMSO-d_6) 11 2 (br s, 1) , 7 9 (br s, 2), 7.3 (m, 3), 7 1 (s, 2), 5 2 (d, 1), 4.9 (s, 2), 4 3 (m, 3), 3 9-3 4 (m, 9), 2 8 (m, 1), 1 4-1 2 (m, 6) ppm;

(*trans*)-1-((5-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 2 (br d, 1), 7 9 (dd, 2), 7 6 (m,

1), 7 3 (t, 2), 6 6 (q, 2), 5.3 (d, 1), 5 0 (s, 2), 4 3 (m, 3), 3 8 (s, 3), 3 4 (m, 3), 2.8 (m, 1), 2 6 (s, 3), 1 5-1.2 (m, 6) ppm,

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10.8 (br d, 1), 9.1 (br s, 1), 7 9 (d, 1), 7.8 (br s, 2), 7 4 (t, 1), 7 2 (m, 3), 7 0 (t, 1), 5 2 (d, 1), 5.0 (m, 2), 4. 3 (m, 3), 3.9-3.4 (m, 7), 2 8 (dd, 1), 14-1.2 (m, 6) ppm,

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10 0 (br s), 7.7 (m, 3), 7 4 (t, 1), 7.3 (t, 2), 7.0 (dd, 2), 5 0 (m, 2), 4.5 (m, 1), 4 2 (m, 5), 3.8 (q, 1), 3 6 (t, 2), 3.4 (m, 2) , 2 9 (m, 1), 1.3 (m, 3), 1.2 (m, 3) ppm,

(*trans*)-1- ((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10 5 (br d, 1), 7 8 (t, 2), 7 3 (t, 2), 6 9 (m, 4), 4.8 (m, 3), 4.4 (m, 1), 4 3 (m, 2), 3 9 (m, 3), 3.6 (m, 3), 3 4 (m, 1), 2 8 (m, 1), 1 4 (m, 3), 1 2 (m, 3) ppm;

(*trans*)-1-((2-acetyl-4,5-dimethylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10 4 (br s, 1), 7 8 (m, 2), 7.4 (s, 1), 7.2 (t, 2), 6 8 (m, 1), 5 2 (d, 1), 4 9 (s, 2), 4 3 (m, 3), 3 8 (m, 1), 3 6 (m, 1), 3 4 (m, 1), 2 8 (m, 1), 2.6 (s, 3), 2 2 (s, 3), 2 1 (s, 3), 1 4 (m, 3), 1.2 (m, 3) ppm,

(*trans*)-1-((5-methoxy-2-(methoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 0 (br d, 1), 7.9 (br s, 2), 7 7 (d, 1), 7 3 (m, 2), 6 6 (m, 2), 5 0 (m, 3), 4 3 (m, 3), 3 8 (s, 3), 3 7 (s, 3), 3 6 (m, 1), 3 4 (m, 2), 2 8 (dd, 1), 1 4 (dd, 3), 1 2 (dd, 3) ppm;

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine, NMR (DMSO-d_6) 7 4 (t, 2), 7 15 (t, 2), 7. 1 (d, 2), 6 6 (d, 2), 5.8 (t, 1), 4 5 (m, 1), 4 2 (m, 1), 3 9 (m, 1), 3 7 (m, 1), 3.4 (m, 1), 3.3 (m, 1), 2.9 (m, 1), 2 8 (d, 1), 2.6 (d, 1), 2 0 (m, 2), 1 3 (d, 1 5), 1 1 (d, 1 5) ppm,

(*trans*)-1- ((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 6 (d, 1), 7 4 (d, 1), 7 3 (m, 2), 7.0 (m, 3), 6 8 (s, 1), 6.3 (d, 1), 4.7 (m, 3), 4.1 (m, 1) , 3 6 (m, 3), 3 0 (br s, 1), 2 7 (br d, 1), 2.2 (d, 1), 1 3 (m, 3), 1.0 (m, 3) ppm,

(*trans*)-1-((2-chloro-4-carboxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((1-nitroso-3,6-di(hydroxysulfonyl)naphthalen-2-yloxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-nitroso-4-hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,6-di(hydroxysulfonyl)naphthalen-1- yloxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-hydroxysulfonyl-6-aminonaphthalen-1-yloxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((3-hydroxysulfonyl-7-aminonaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((5- hydroxysulfonylquinolin-8-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-dinitro-7- hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-4- hydroxysulfonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-amino-4-hydroxysulfonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-formyl-2,6-di-*t*-butylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4- (morpholin-4-yl)methyl-2,5-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((4- (methoxycarbonyl)-2,6-dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((4-(hydroxysulfonyl) naphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3,6-di(hydoxysulfonyl)-8- aminonaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-5-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-trifluromethyl-2,3,5,6,-tetrafluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- methoxy-4-formyl-5-(2-hydroxy-3-methoxy-5-formylphenyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-carboxy-2,3,5,6-tetrafluorophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-(adamant-1-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-(adamant-1-yl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-di((1-methyl-1-phenyl)ethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-acetyl-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-*t*- butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-acetyl-4-chloro-5-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-acetyl-4-chloro-6-nitrophenxoy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-acetyl-4,6- dibromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-formyl-4,6-di(*t*-butyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((3,5-dinitrophenoxy)methyl)carbonyl-2,5-dimethyt-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2,6-dichloro-4- ethoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-ethoxycarbonyl-4-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-6-(prop-3-enyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- fluoro-4-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-acetyl-4-methyl-6-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methylbenzothiazol-5-yloxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-(4-(trifluoromethyl)phenoxy)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-(1*H*-pyrazol-3-yl)-4-chloro-5-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2- (1*H*-pyrazol-3-yl)-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(((2-phenyl-4-oxo-7- hydroxy-4*H*-1-benzopyran-3-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2-chloro-3- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-methoxy-4-(butoxymethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((6-hydroxyquinolin-2-yloxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(*trans*)-1-((2-methoxycarbonyl- 6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((2,5-di(*t*-butyl)-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-formyl-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(2 *H*-benzotriazol-2-yl)-4-(2-hydroxyethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(methylthio)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5- di(*t*-butyl)-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5-dibromo-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-diiodo-4-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- nitro-4-methoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(ethoxycarbonyl)indol-5-yloxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((3-(2-carboxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dinitro-4- (carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-3-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((6-carboxynaphthalen-2-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-difluoro-4- ethylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(2-(methoxycarbonyl)ethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(prop-3-enyl)-4-acetylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((3- oxo-2*H*- benzofuran-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4,6-tribromo-3,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(heptylcarbonyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- carboxy-4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-nitro-4-phenylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-methoxy-4-(eth-2-enyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-chloro-4- methoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,6-diiodo-4-cyanophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-diiodo-4-carboxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2- phenyl-4-oxo-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2-phenyl-4-oxo- 7-methoxy-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-(((2-phenyl-4-oxo-7- methoxy-2,3-dihydro-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

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(trans)-1-((4- octylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((4-phthalimid-1-ylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((3-(morpholin-4-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-chloro-4- bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2-oxo-7-methoxy-2*H*-1-benzopyran-8-yl) oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-5-fluorophenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-(1- methylcyclohex-1-yl)-4-methyl-6-(2-hydroxy-3-(1-methylcyclohex-1-yl)-5- methylbenzyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((2-formyl-3-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4-carboxy-6- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dimethyl-4-carboxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-(2-(carboxy)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethoxy-4-(hydroxymethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,6-dibromo-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4- (ethoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-amino-4-(methoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-(4-nitrophenyl)eth-2-enyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-acetyl-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-di(*t*- butyl)-4-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4- (ethoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2-cyclohexyl-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dimethyl-4-chlorophenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-ethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-*n*-butylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-(((3-carboxy-1-bromonaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- bromo-4-nitro-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dichloro-4-(ethoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((4-methyl-2-oxo-2*H*-1-benzopyran- 6-yl) oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-dibromo-4-formyl-6-methoxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4- (2-(4-nitrophenyl)eth-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2,4,6-tribromo-3- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-benzyl-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2- (bezothiazol-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-nitro-6-fluorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-ethoxy-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-bromo-4,6-di(*t*-butyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(pyrrolidin-1-yl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-(morpholin-4-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(piperidin-1-yl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-formyl-4-chloro-6-bromophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((4,7- dimethoxy-5-formylbenzofuran-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-4-methyl-8- nitro-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4- bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-chloro-4-bromo-6-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dimethyl-6-*t*-butylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-(((2-nitro-4-(hydroxysulfonyl)naphthalen-1-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- (hydroxysulfonyl)-6-aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- (hydroxysulfonyl)-7-aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- (methoxycarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-*n*-butylcarbonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-ethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(((2-ethyl)hexoxy) carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-((*n*-pentoxy)carbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-5-(methoxycarbonyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2, 4,6-tribromo-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-methoxy-4-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(2- (phenyl)eth-2-enyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-(1,2,4-triazol-1-yl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-4-chloro-5-methylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(*n*-hexoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-chloro-4- formyl-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methoxy-4-(2-(ethoxycarbonyl) ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3,4,6-tetrachlorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- ((2-methylpropoxy)carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2-(*n*- butoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-(phenylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-hydroxymethyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-mercaptophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

(trans)-1-((2-nitro-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4-di(1-methylbutyl) phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-trifluoromethyl-4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6- dibromo-4-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2,4-dichloro-6- acetyl)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxycarbonyl-4-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- formyl-4-bromo-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2,6-diformyl-4-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2, 6-dinitro-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-4-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-formyl-4-nitro-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(aminocarbonyl) methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxycarbonyl-4-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-(((2-phenyl-4-oxo-4*H*-1-benzopyran-6-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- chloro-4-trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-3-methyl-6- isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((5,7-dibromo-2-methylquinolin-8- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5,7-dichloro-2-methylquinolin-8-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

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(trans) -1-((2,6-dinitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-4-(1,1-dimethylpropyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,6-diphenyl-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4-dichloro-3- methyl-6-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-4-(carboxy)methyl-2*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((2-oxo-4-trifluoromethyl-2*H* -1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-d imethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-*t*-butyl-4-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-formyl-6-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxycarbonyl- 4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-bromo-5-fluorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4- di(1,1-dimethylpropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methyl-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3,4-trifluorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5- difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-5-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2- methyl-3-(ethoxycarbonyl)indol-5-yl)oxy)methyl)carbonyl-2, 5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-aminocarbonyl-4- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dinitro-3-*t*-butylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-fluoro-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-3- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(2-ethylhexoxy)carbonylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2,4,6-tribromo-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((4-(4-bromophenyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(4- carboxypheny)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,3,6-trifluorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2,4,5-trifluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,6- trifluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-fluoro-5-trifluoromethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2,4-dinitronaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((3,6- di(hydroxysulfonyl)-8-aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- acetyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,6-dimethyl-4-(1-(3,5-dimethyl-4- hydoxyphenyl)-1-methylethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(3-(4- hydroxyphenyl)hex-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-(((6-(hydroxysulfonyl) naphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-chloro-4-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-bromo-4,5-difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-chloro-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(2- (methoxycarbony)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2,6-diphenyl-4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- amino-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-methyl-4-fluorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methyl-4-iodophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-fluoro-6- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-3-isopropyl-6-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-carboxy-3,4,6-trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-6- isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(pipendin-1-yl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2,3-dihydro-2,2-dimethylbenzofuran-7-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-di(*t*-butyl)-4-(1-methylpropyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-methyl-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((phenanthren-9-yl) oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-fluoro-3- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-nitro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-chloro-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-4-bromo-6- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-(acetyl)methylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-(5-mercaptotetrazol-1-yl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4,6-triiodo-3- (2-carboxy)butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3-hydroxymethyl-4-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,3,5,6-tetrafluoro-4-(2,3,4,5,6-pentafluorophenyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(benzotriazol-2-yl)-4,6-di(1,1-dimethylpropyl) phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenyl-3-hydroxy-4-oxo-4*H*-1-benzopyran-6- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((indanonyl)oxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-nitro-3-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-(2,4-dinitrophenyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-methyl-4- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dibromo-4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6- diiodo-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine:

(trans)-1-((2-formyl-4-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-amino-5-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-amino-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- amino-4-*t*-butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methyl-3-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- carboxy-5-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3-methyl-4-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2,5-dimethyl-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dibromo-4- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- aminocarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-aminocarbonyl-4-chlorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4,6- tri(dimethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-hydroxymethyl-6-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,3-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(methoxycarbonyl)- 5-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methoxy-4-(methoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dimethoxy-4-(prop-3-enyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-acetyl-5-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-acetyl-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-acetyl-3-methoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- methoxy-4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,6-dimethoxy-4-acetylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-di(*t*-butyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4- di(*t*-butyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3,5-di(*t*-butyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-di(isopropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4- (ethoxycarbony)methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-1-((2-ethoxy-5-prop-2- enylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-5-prop-2-enylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2,6-di(1-methylpropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-difluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-diphenylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-3- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-cyclopentyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-cyclopentylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,3-difluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans)*-1-((2-carboxy-6-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- amino-4-chloro-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,4-difluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-6-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2,4- dicarboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,3-dimethoxy-5-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-bromo-4-fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dichoro-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-methyl-4-isopropylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1- (((fluoren-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-diethylaminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)- 1-((2-amino-3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2-oxo-3,4,8- trimethyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-acetyl-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-fluoro-4-bromophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- (methylcarbonyl)amino-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((1-acetylnaphthalen- 2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-4-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- methyl-5-isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-4-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((1- aminonaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-aminonaphthalen-1-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-methoxy-4-(1,2-dihydroxyethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3-(2- aminoethyl)indolin-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5-chloroquinolin-8- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-4-(2-(amino)ethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-(2-(amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-4-(2- (amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,4-diaminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(diethylamino)methyl-4- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methyl-5-(2-aminobutyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-(benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-bromo-6-fluorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- iodophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(2-carboxyethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6- dibromo-3-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,6-dichloro-3-carboxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dimethoxy-4- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(2-carboxyethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(2- hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3-(2-hydroxyethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-(2-hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-4-(2- hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,4-dibromo-6-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-fluoro-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dichloro-6- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-diiodo-6-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- methoxy-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-ethoxy-6-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-5-(diethylamino)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-formyl-5-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-formyl-4-bromophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-formyl-4-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((4-methoxynapthalen- 1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-5,6-dimethoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- nitro-4-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((fluoren-9-on-1-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((4-hydroxy-1,2,3,4-tetrahydronaphthalen-8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2, 3,4,5,6-pentabromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-methyl-3,4,5,6- tetrabromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,3,4-trichlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-methyl-4-bromo-6-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-chloro-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4,6-triiodophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- formyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((1-bromonaphthalen-2-yl)oxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((1,6- dibromonapthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((1-nitrosonaphthalen-2-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2,4-dichloronaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2- nitronaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-carboxynaphthalen-1-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2-methylnaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-(((3- (hydroxysulfonyl)-7-(dimethylamino)naphthalen-1-yl)oxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((4- methoxynaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((1-formylnapthalen-2-yl)oxy) methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1-carboxynaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((1- amino-4-(hydroxysulfonyl)naphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(naphthalen-2- yl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((3-aminonaphthalen-2-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- fluoro-4-(carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4-(carboxymethyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methoxy-4-(carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4- hydroxymethylphenxoy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(hydroxymethyl)-4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-di(hydroxymethyl)-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- methoxy-4-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((4-mercaptophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2-carboxyindol-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-(((3-carboxyindol-5- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((indol-4-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((indol-5-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(benzoxazol-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-(((2-methylquinolin- 8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((5,7-dibromoquinolin-8-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5,7- diiodoquinolin-8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((5-nitroquinolin-8-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-(((quinolin-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((5-(hydroxysulfonyl)- 7-iodoquinolin-8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-carboxy-2,5,7,8-tetramethyl-2,3- dihydro-1- benzopyran-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-3-chloro-4-methyl-2*H* -1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-3-(diethylamino)methyl)-4- methyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-6-methoxy-2 *H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-2*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-methoxy-4-formyl-6-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-formyl-6-iodophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- methoxy-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-ethoxy-4-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-carboxy-4-formylphenox)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4-dichloro-6- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dinitro-6-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4- dinitro-6-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,4-dinitro-6-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,5-dinitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dinitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- nitro-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-4-formyl-6-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dinitro-4-methylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- nitro-4-(carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dichlorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methoxy-5-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((4-cyanophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(1-methyl-1-phenylethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- (ethylamino)-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((2-acetylnaphthalen- 1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(carboxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- (carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((benzotriazol-1-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-(((quinolin-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dimethoxy-4-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,4- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4,6-tri(*t*-butyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethoxy-4-(methoxycarbonyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-trifluoromethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-methyl-5- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(4-cyanophenyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- nitro-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-methylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- methylphenox)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(methoxycarbonyl)methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-(((carbazol-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-1,3- benzothiol-2-on-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-3-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((2-oxo-4-methyl-2*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- carboxy-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-methoxy-5-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-(((2-phenyl-4-oxo-2,3-dihydro-4*H*-1-benzopyran-6-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((quinolin-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,3-diaminophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-(((fluorenon-9-on-2-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5,6,7, 8-tetrahydronaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((5,6,7,8- tetrahydronaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(trans)-9-((2,4,6- tribromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dibromo-4-cyanophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine·

(trans)-1-((2,3,5,6-tetrafluorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6- difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-dichlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,3,6- trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine

(trans)-1-((2-chloro-4,5-dimethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5-dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-chloro-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(methylcarbonyl)aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-isopropoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(benzyloxy)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-ethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-phenylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-(ethoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(ethylcarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(*t*-butyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(1-methylpropyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,3-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,3,5- trimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,3,6-trimethylphenxoy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,4-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,4,6-trimethoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methyl-5-isopropylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,5-dimethyl-4-(diethylamino)methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(*t*-butyl)-6-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-prop-3-enyl-6-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-prop-2-enylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-ethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-*n*-propylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((3-fluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5-difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-chloro-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dichlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- iodophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-(phenylamino)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- (diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3-phenylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-trifluoromethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- *t*-butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-isopropylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((3-methyl-4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,4-dimethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-*t*-butyl-5-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- isopropyl-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-ethylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6- dimethyl-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,6-dibromo-4-fluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-bromo-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-isopropyl-4-chloro-5-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(methylcarbonyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-ethoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-propoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-*n*- butoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-*n*-hexoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4- *n*-heptoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(propoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(ethylcarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(1,1,3,3-tetramethylbutyl)phenoxy) methyl) carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(1,1-dimethylpropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(1-methylpropyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- acetyl-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(*t*-butyl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-(ethylamino)-4-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(methoxycarbonyl)methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-ethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-*n*-propylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4,6-dibromophenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-4,6- dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4,6-diiodophenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- carboxy-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-carboxy-6-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-carboxy-5-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-5-methoxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- carboxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-4-bromophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-carboxy-4-fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-carboxy-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4-iodophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- carboxy-4-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-chlorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,3, 4-trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,3,4,5,6-pentachlorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,5-trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((3-(ethoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dimethyl-4- bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5-dimethyl-4-bromophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- methyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-isopropyl-4-chloro-5-methylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-ethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(*t*-butyl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-formyl-4-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-prop-3-enylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(1-phenyethyl)-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(ethoxycarbonyl)methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-trifluoromethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-fluoro-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-fluoro-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((7- methoxynaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-benzyloxy-4-cyanophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-bromo-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3,5-dimethoxy-4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-dibromo-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dimethoxyphenoxy)methyl)carbonyl-2, 5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- nitro-3-carboxy-6-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-cyanophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-5- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-(carboxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-5-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(dimethylamino)methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-(dimethylamino)ethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((naphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5- aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-nitro-4-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2,6-di(*t*-butyl)-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- carboxy-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-5-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-nitro-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(benzyloxy)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

(trans)-1-((3,5- di(trifluoromethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4-dibromophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dibromo-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2,4-dichlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3,5-dimethyl-4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dicarboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dichloro-4-carboxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2- carboxyquinolin-4-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-dimethyl-4-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-di(*t*-butyl)-4-carboxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- amino-5-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-di(*t*-butyl)-4- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-(((4-carboxyquinolin-2-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-nitro-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-ethyl-4-chloro-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5-di(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-(morpholin-4-yl)methyl-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-cyanophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- chloro-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-trifluoromethylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-4-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-(dimethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3-methyl-4- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5-dimethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- phenylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(ethoxycarbonyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4-benzylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-4- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3-carboxynaphthalen-2-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((quinolin-8-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((3-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-(cyclohexyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((quinolin-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dichloro-3-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2, 5-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-bromophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- (methylcarbonyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-acetylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-5- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-(((tropinon-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-5- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-nitro-5-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- formyl-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-5-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((2-amino-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-amino-3- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6- dichloro-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((3-fluoro-4-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,3-difluoro-6-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-cyanophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- bromo-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-chlorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,4-dichlorophenoxy)methyl)carbonyl-2, 5- dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5- dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,4,5-trimethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3,5-dimethyl-4-chlorophenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(methoxycarbonyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-*t*-butylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((naphthalen-2-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((6-bromonaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-methoxy-5-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1,3-benzodioxolan-5-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dimethyl-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- methoxy-4-(amino)methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((3-(aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-ffluorobenzyl)piperazine,

(trans)-1-((3-(methoxycarbonyl)methylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(4-phenylcarbonyl)-4-fluorophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-(1-methyl)cyclohexyl-2,4-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- (benzyloxycarbanyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(4-(methyl)phenylcarbonyl)-5- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-phenylcarbonyl-5-octoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-octylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(2-(carboxy)phenylcarbonyl-5- di(*n*-butyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonyl-5- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-methoxy-4-(3-hydroxyprop-2-enyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3-(phenylaminocarbonyl)naphthalen-2-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((6-(phenylcarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-((2- phenylethyl)carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((4-((4-fluorophenyl) carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(phenylamino)carbonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2-phenylcarbonyl-4- chloro-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((4-(4-chlorophenyl)carbonylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans) -1-((4-benzylcarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonyl-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-methylcarbonylethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-phenylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(trans)-1-((3- phenylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine

C. In a similar manner, the following compounds of formula (Ib) were made:

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.6 (m, 3), 7.5 (m, 4), 6 2 (s, 2), 4.6 (m, 4), 4.2 (m, 4), 3.8 (m, 9), 3 4 (m, 1), 2.6 (m, 1) ppm,

1-((3- methoxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 5), 6.5 (m, 4), 4 6 (s, 2), 3.8-3.5 (m, 9), 2. 4 (m, 4) ppm,

1-((3,4-dimethoxyphenoxy)methyl)carbonyl-4-(benzyl) piperazine; NMR ($CDCl_3$) 7.8 (m, 2), 7.4 (m, 3), 6.8 (d, 1), 6 6 (d, 1), 6 4 (dd, 1), 4.8 (d, 2), 4.3 (m, 3), 4 0 (m, 1), 3 7 (s, 3), 3.65 (s, 3), 3 6-3 3 (m, 8), 3.2-2.9 (m, 3) ppm,

1- ((phenoxy)methyl)carbonyl-4-(benzyl)piperazine and 1-(chloro)acetyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 7), 7.0 (m, 3) , 4 7 (s, 2), 3.6 (m, 6), 2 4 (m, 4) ppm;

1-((4-chlorophenoxy) methyl)carbonyl-4-(benzyl)piperazine and 1-(chloro)acetyl-4-(benzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 7), 6.9 (m, 2), 4 6 (s, 2), 3.6 (m, 6), 2.4 (m, 4) ppm;

1-((3-cyanophenoxy)methyl) carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7 0 (m, 4), 6 8 (m, 3), 4 4 (q, 2), 4.2 (d, 1), 3.9 (d, 2), 3 6 (m, 3), 3 0 (m, 3), 2.6 (m, 2) ppm,

1-((4-cyanophenoxy)methyl)carbonyl-4- (benzyl)piperazine; NMR ($CDCl_3$) 7.6 (m, 4), 7.4 (m, 3) , 7 0 (d, 2), 4.9 (q, 2), 4 6 (d, 1), 4 3 (d, 2), 4 0 (d, 2), 3.6 (t, 1), 3 4 (d, 2), 3.0 (m, 2) ppm;

1-((3-(1-methylimidazolin-2yl) phenoxy)methyl)carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7 5 (m, 6), 7.2 (m, 3), 5 0 (d, 2), 4 0 (m, 4), 3.3 (q, 4), 3 0 (m, 6) ppm;

1-((4-chloro-2-aminocarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine, NMR (DMSO-d_6) 8.7 (s, 1), 7 8 (s, 1), 7.7 (s, 1), 7 6 (dd, 1), 7.4 (q, 3), 7.2 (d, 1), 5 0 (s, 2), 3 4 (br d, 4), 3.3 (s, 2), 2 4 (br d, 4) ppm,

1-((5-chloroquinolin- 8-yloxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 9 0 (s, 1), 8.5 (d, 1), 7.75 (dd, 1), 7 65 (d, 1), 7.4 (q, 2), 7.1 (d, 1), 5 1 (s, 2), 3.5 (m, 6), 2.4 (br d, 4) ppm,

1- ((3-trifluoromethoxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-(3-(3,4,5-trimethoxyphenoxy)propyl)carbonyl-4-(benzyl)piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)propyl)carbonyl-4-(benzyl) piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)pentyl)carbonyl-4- (benzyl) piperazine;

1-((4-methoxyphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((3-chlorophenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)ethyl)carbonyl- 4-(benzyl) piperazine;

1-((3,4-dichlorophenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((3,5-dichlorophenoxy)methyl)carbonyl-4- (benzyl)piperazine,

1-((3,4,5-trimethylphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((4-nitrophenoxy)methyl)carbonyl-4-(benzyl) piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)septyl)carbonyl-4- (benzyl) piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)-2- methylpropyl)carbonyl-4-(benzyl)piperazine;

1-(1-(3,4,5- trimethoxyphenoxy)butyl)carbonyl-4-(benzyl)piperazine,

1-((4- bromophenoxy)methyl)carbonyl-4-(benzyl)piperazine,

1-((4- fluorophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- trifluoromethylphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1- (((4-chlorophenyl)thio)methyl)carbonyl-4-(benzyl)piperazine;

1- ((2-chlorophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (benzyloxy)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (methoxycarbonyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1- ((4-(amino)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- hydroxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine,

1-((4-(1- methylethyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4-(2,2-dimethylethyl)phenoxy)methyl)carbonyl-4- (benzyl) piperazine,

1-((4-(acetyl)phenoxy)methyl)carbonyl-4-(benzyl) piperazine;

1-((napthalenyl-2-oxy)methyl)carbonyl-4-(benzyl) piperazine,

1-((4-chloro-3,5-dimethylphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((1,3-benzodioxolyl-5-oxy)methyl)carbonyl- 4-(benzyl)piperazine;

1-((2,4,6-trichlorophenoxy)methyl)carbonyl- 4-(benzyl)piperazine;

1-((2,3,4,5,6-pentafluorophenoxy)methyl) carbonyl-4-(benzyl)piperazine;

1-((2-(benzyloxy)-4-cyanophenoxy) methyl)carbonyl-4-(benzyl)piperazine,

1-((2-chloro-4- bromophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((3- bromophenoxy)methyl)carbonyl-4-(benzyl)piperazine,

1-((3,5- trifluoromethylphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1- (((5-oxo-6,7,8-trihydronaphthalen-1-yl)oxy)methyl)carbonyl-4-(benzyl) piperazine,

1-(((2-oxo-2*H*-1-benzopyran-4-yl)oxy)methy) carbonyl-4-(benzyl)piperazine,

1-((2-cyanophenoxy)methyl) carbonyl-4-(benzyl)piperazine;

1-((4-methyl-3,5-dibromophenoxy) methyl)carbonyl-4-(benzyl)piperazine,

1-((quinolinyl-6-oxy) methyl)carbonyl-4-(benzyl)piperazine,

1-(((diphenyl)methoxy) methyl)carbonyl-4-(benzyl)piperazine,

1-((3-(morpholin-4-yl) phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((2-bromophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine, hydrochloride salt,

1-((pyridinyl-3-oxy)methyl)carbonyl-4-(benzyl)piperazine,

1- ((2-(benzyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (benzyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (formyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine,

1-((2- (prop-3-enyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,6-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((benzothiazolyl-2-oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((4-cyclohexylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((4-(benzyloxy)carbonylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((5-chloroquinolinyl-8- oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((4- (imidazol-1-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-chloro-5-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((4-carboxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4-iodophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 7 6 (m, 6), 6 8 (d, 2), 4.9 (d, 2), 4.4 (m, 3), 4.0 (m, 1), 3 6 (m, 1), 3.4-2.9 (m, 6) ppm;

1-((2-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dimethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((2-methylquinolinyl-4-oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2,3-dihydro-1*H*-inden-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((coumarin-4-yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((4-chlorobenzyloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-(((4-chlorophenyl)amino)methyl)carbonyl-4-(4-chlorobenzyl) piperazine, hydrochloride salt; NMR (DMSO-d_6) 11.4 (br s, 1), 7.6 (dd, 4), 7 1 (d, 2), 6.6 (d, 2), 4 4 (m, 4), 4.0 (m, 4); 3 6-2.9 (m, 4) ppm;

1-((4-chloronaphthalenyl-1-oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-(((4-chlorophenyl)(methyl)amino) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-(((di(4-chloro) phenyl)methoxy)methyl)carbonyl-4-(chlorobenzyl)piperazine,

1-((3, 5-dimethoxy-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine, NMR ($CDCl_3$) 7.2 (q, 4), 6.2 (s, 2), 4 7 (s, 2), 3.9 (s, 6), 3.6 (m, 4), 3.5 (s, 2), 2 4 (m, 4) ppm;

1-((5,7- dichloroquinolinyl-8-oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((6-hydroxycoumarin-4-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-fluoro-4-chlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine, hydrochloride salt; NMR (DMSO- d_6) 11.8 (s, 1), 7.5 (m, 5), 7.1 (d, 1), 6 8 (d, 1), 5 0 (q, 2) , 4 3 (m, 3), 3.9 (m, 1), 3.6-2.9 (m, 6) ppm,

1-((2- (hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,4-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,4-dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine, NMR (DMSO-d_6) 7.6 (m, 6), 7. 3 (d, 1), 5 0 (q, 2), 4.3 (m, 3), 3.9 (m, 1), 3 5-2.9 (m, 6) ppm,

1-((4-bromo-2-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine; NMR (DMSO-d_6) 11 4 (br s, 1), 7.8 (m, 2), 7 5 (m, 4), 7 2 (d, 1), 5 2 (q, 2), 4.4 (m, 3), 4.0 (m, 1), 3.6-2.9 (m, 6) ppm;

1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine,

1-((4-bromo-2-chlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine hydrochloride salt;

1-((2- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine hydrochloride salt,

1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine hydrochloride salt;

1-((2-aminocarbonyl-4- chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO- d_6) 8.7 (br s, 1), 7 8 (s, 1), 7.7 (s, 1), 7.6 (dd, 1) , 7 2 (m, 3), 7.2 (d, 1), 5.0 (s, 2), 3 5 (m, 6), 2.4 (m, 4) ppm,

1-((3,5-dimethoxy-4-bromophenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 6.2 (s, 2), 4.7 (s, 2), 3.9 (s, 6), 3.6 (m, 4), 3.5(s, 2), 2 4 (m, 4) ppm;

1-((3- formyl-4-nitrophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10 5 (s, 1), 8 2 (d, 1), 7 3 (m, 6), 4.9 (s, 2), 3.6 (m, 2), 3.5 (m, 4), 2.4 (m, 4) ppm,

1-((2-chloro-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((1-nitroso-3,6-di(hydroxysulfonyl)naphthalen-2-yloxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-nitroso-4- hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((3,6-di(hydroxysulfonyl)naphthalen-1-yloxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-hydroxysulfonyl-6- aminonaphthalen-1-yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-hydroxysulfonyl-7-aminonaphthalen-1-yloxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,

1-((5-hydroxysulfonylquinolin-8- yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,3- dinitro-7-hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-carboxy-4-hydroxysulfonylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-4- hydroxysulfonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-formyl-2,6-di-*t*-butylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((4-(morpholin-4-yl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- (methoxycarbonyl)-2,6-dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-(hydroxysulfonyl)naphthalen-1-yloxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,6-di(hydoxysulfonyl)-8-aminonaphthalen-1-yloxy) methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-5- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((4- trifluromethyl-2,3,5,6,-tetrafluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-formyl-5-(2-hydroxy-3- methoxy-5-formylphenyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-carboxy-2,3,5,6-tetrafluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(adamant-1-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- (adamant-1-yl)-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4-di((1-methyl-1-phenyl)ethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-acetyl-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- nitro-4-*t*-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-acetyl-4-chloro-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-acetyl-4-chloro-6- nitrophenxoy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- acetyl-4,6-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-4,6-di(*t*-butyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((3,5-dinitrophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((2,6-dichloro-4- ethoxycarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-ethoxycarbonyl-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-methoxy-6-(prop-3-enyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-fluoro-4- cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- acetyl-4-methyl-6-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-methylbenzothiazol-5-yloxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-carboxy-4-(hydroxysulfonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-(4- (trifluoromethyl)phenoxy)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-(1*H*-pyrazol-3-yl)-4-chloro-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- ((2-(1*H*-pyrazol-3-yl)-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-(((2-phenyl-4-oxo-7-hydroxy-4*H*- 1-benzopyran-3-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-chloro-3-trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(butoxymethyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((6-hydroxyquinolin-2-yloxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxycarbonyl-6- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- ((2,5-di(*t*-butyl)-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-formyl-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-(2*H*- benzotriazol-2-yl)-4-(2-hydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,

1-((2-(methylthio)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((3,5-di(*t*-butyl) -4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((3,5-dibromo-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-diiodo-4-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((2-nitro-4-methoxycarbonylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2- (ethoxycarbonyl)indol-5-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((3-(2-carboxyethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,6-dinitro-4-(carboxymethyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2- nitro-3-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((6-carboxynaphthalen-2-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2,6-difluoro-4-ethylcarbonylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(2-(methoxycarbonyl) ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-(prop-3-enyl)-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-(((3-oxo-2*H*-benzofuran-6-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4,6-tribromo-3,5- dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((4-(heptylcarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-carboxy-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-nitro-4-phenylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-methoxy-4-(eth-2-enyl)phenoxy) methyl)carbonyl-4-(4-chlorobenryl)piperazine;
1-((2-chloro-4- methoxycarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,6-diiodo-4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,6-diiodo-4-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((2-phenyl-4-oxo-7-methoxy-4*H*-1-benzopyran-5-yl) oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-phenyl-4- oxo-7-methoxy-2,3-dihydro-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((4-octylcarbonylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((4-phthalimid-1- yiphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- (morpholin-4-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-chloro-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((2-oxo-7-methoxy-2*H*-1-benzopyran-8-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-acetyl-5- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-(1-methylcyclohex-1-yl)-4-methyl-6-(2-hydroxy-3-(1-methylcyclohex-1- yl)-5-methylbenzyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-formyl-3-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-chloro-4-carboxy-6-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethyl-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-4-(2-(carboxy)ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dimethoxy-4-(hydroxymethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dibromo-4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-nitro-4-(ethoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-amino-4-(methoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(2-(4-nitrophenyl) eth-2-enyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-acetyl-3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2,6-di(*t*-butyl)-4-(methoxycarbonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- methoxy-4-(ethoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-cyclohexyl-4-chlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-((2,6-dimethyl-4-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4- ethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- *n*-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((3-carboxy-1-bromonaphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-bromo-4-nitro-6-formylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-4-chlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine,
1-((2,6-dichloro-4-(ethoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((4-methyl-2-oxo-2 *H*-1-benzopyran-6-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3-dibromo-4-formyl-6-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-(2-(4-nitrophenyl)eth-2-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,4,6- tribromo-3-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-benzyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-(bezothiazol-2-yl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-nitro-6-fluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-ethoxy-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-bromo-4,6-di(*t*-butyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-(pyrrolidin-1-yl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-(morpholin-4-yl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-(piperidin-1-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- formyl-4-chloro-6-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((4,7-dimethoxy-5-formylbenzofuran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-oxo-4- methyl-8-nitro-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-bromophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-bromo-6- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2,4-dimethyl-6-*t*-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((2-nitro-4-(hydroxysulfonyl)naphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((3- (hydroxysulfonyl)-6-aminonaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((3-(hydroxysulfonyl)-7- aminonaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3-(methoxycarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4-(hydroxysulfonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- *n*-butylcarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-ethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-(((2-ethyl)hexoxy)carbonyl)phenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((4-((*n*-pentoxy)carbonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- nitro-5-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2,4,6-tribromo-3-methylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-methoxy-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-methoxy-4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((4-(2-(phenyl)eth-2-enyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-(1,2,4-triazol-1-yl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-nitro-4-chloro-5-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(*n*- hexoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-formyl-6-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-(2-(ethoxycarbonyl) ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,3,4,6-tetrachlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-((2-methylpropoxy)carbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(*n*-butoxycarbonyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(phenylamino) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- hydroxymethyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-mercaptophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((2-nitro-6-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-di(1-methylbutyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- trifluoromethyl-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,6-dibromo-4-(methoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-dichloro-6-acetyl) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- methoxycarbonyl-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-formyl-4-bromo-6-methoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-diformyl-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2,6-dinitro-4-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-nitro-4-acetylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-formyl-4-nitro-6-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- (aminocarbonyl)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxycarbonyl-4-methoxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-6-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-3-methyl-6- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- (((5,7-dibromo-2-methylquinolin-8-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((5,7-dichloro-2-methylquinolin-8-yl) oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6- dinitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-nitro-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-amino-4-(1,1-dimethylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-Biphenyl-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-dichloro-3-methyl- 6-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- (((2-oxo-4-(carboxy)methyl-2*H*-1-benzopyran-7-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-oxo-4- trifluoromethyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-*t*-butyl-4-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-6- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxycarbonyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-bromo-5-fluorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,4-di(1,1-dimethylpropyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-methyl-4- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2,3,4-trifluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,5-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-methyl-5-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-(((2-methyl-3-(ethoxycarbonyl)indol-5- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- aminocarbonyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2,6-dinitro-3-*t*-butylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-fluoro-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- carboxy-3-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(2-ethylhexoxy)carbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,4,6-tribromo-4-carboxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(4-bromophenyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((4-(4-carboxypheny)phenoxy)methyl)carbanyl-4-(4- chlorobenzyl)piperazine,
1-((2,3,6-trifluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4,5- trifluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2,4,6-trifluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-fluoro-5-trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((2,4-dinitronaphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3,6- di(hydroxysulfonyl)-8-aminonaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-acetyl-4-chlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethyl-4-(1-(3, 5-dimethyl-4-hydoxyphenyl)-1-methylethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((4-(3-(4-hydroxyphenyl)hex-2-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((6- (hydroxysulfonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-chloro-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-bromo-4,5-difluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-methoxy-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-(2-(methoxycarbony)ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,6-diphenyl-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-amino-3- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methyl-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine
1-((2-methyl-4-iodophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-fluoro-6-methoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-carboxy-3-isopropyl-6- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-carboxy-3,4,6-trichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-carboxy-6-isopropylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-((2-(piperidin-1-yl)-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- (((2,3-dihydro-2,2-dimethylbenzofuran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-di(*t*-butyl)-4-(1- methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-methyl-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-(((phenanthren-9-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((2-nitro-4-bromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-fluoro-3-trifluoromethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-nitro-5- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-chloro-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-4-bromo-6-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-(acetyl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(5- mercaptotetrazol-1-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4,6-triiodo-3-(2-carboxy)butylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-hydroxymethyl-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2, 3,5,6-tetrafluoro-4-(2,3,4,5,6-pentafluorophenyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-(benzotriazol-2-yl)-4,6-di(1, 1-dimethylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-phenyl-3-hydroxy-4-oxo-4*H*-1-benzopyran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((indanonyl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-nitro-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-nitro-3-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-(2,4-dinitrophenyl)aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((3-methyl-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2, 6-dibromo-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-diiodo-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-formyl-4-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-amino-5-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-amino-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-amino-4-*t*-butylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,

1-((2-amino-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methyl-3-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((2-carboxy-5-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((3-methyl-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,5-dimethyl-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2, 6-dibromo-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2-aminocarbonylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-aminocarbonyl-4-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(2- aminoethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,4,6-tri(dimethylamino)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2-hydroxymethyl-6-methoxyphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,

1-((2,3-dimethoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((4-(methoxycarbonyl)-5- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-methoxy-4-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2,6-dimethoxy-4-(prop-3-enyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-5- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-acetyl-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-3-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-methoxy-4-acetylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,6-dimethoxy-4-acetylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-di(*t* -butyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- ((2,4-di(*t*-butyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((3,5-di(*t*-butyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2,6-di(isopropyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-methoxy-4- (ethoxycarbony)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-ethoxy-5-prop-2-enylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-5-prop-2-enylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-di(1- methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,4-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-diphenylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2-nitro-3-trifluoromethylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,

1-((2-cyclopentyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-cyclopentylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,3-difluorophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-6-aminophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-amino-4- chloro-5-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,4-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-carboxy-6-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,4-dicarboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((2,3-dimethoxy-5-formylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-bromo-4- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- ((2,6-dichoro-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((3-methyl-4-isopropylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-(((fluoren-2-yl)oxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-diethylaminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-amino-3- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- (((2-oxo-3,4,8-trimethyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-4-fluorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-fluoro-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2- (methylcarbonyl)amino-5-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-(((1-acetylnaphthalen-2-yl)oxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-methoxy-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((3-methyl-5- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- ((2-methyl-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((1-aminonaphthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((4-aminonaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-methoxy-4-(1,2- dihydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((3-(2-aminoethyl)indalin-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((5-chloroquinolin-8-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-methoxy-4-(2-(amino) ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((4-(2-(amino)ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(2-(amino)ethyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2,4-diaminophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,

1-((4-aminophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,

1-((2-(diethylamino)methyl-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2- methyl-5-(2-aminobutyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2-(benzotriazol-2-yl)-4-(1,1,3,3- tetramethylbutyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-nitro-4-bromo-6-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-iodophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((2-(2-carboxyethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-carboxy-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,6-dibromo-3-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dichloro-3-carboxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,

1-((2-methoxy-4-carboxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dimethoxy- 4-carboxyphenoxylmethyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((4-(2-carboxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(2-hydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3-(2-hydroxyethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((4-(2-hydroxyethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-methoxy-4-(2- hydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,4-dibromo-6-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-fluoro-6-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((2,4-dichloro-6-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-diiodo-6- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-methoxy-6-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-ethoxy-6-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2-formyl-5-(diethylamino)phenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-formyl-5-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-formyl-3,5- dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine ,

1-((2-formyl-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-formyl-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-(((4-methoxynapthalen-1-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-carboxy-5,6-dimethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((3-nitro-4- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- (((fluoren-9-on-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((4-hydroxy-1,2,3,4-tetrahydronaphthalen-8-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3,4,5,6- pentabromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-methyl-3,4,5,6-tetrabromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2,3,4-trichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-methyl-4-bromo-6-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,4,6-triiodophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-(((1-bromonaphthalen-2-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((1,6-dibromonapthalen- 2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((1- nitrosonaphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2,4-dichloronaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-nitronaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-carboxynaphthalen- 1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2- methylnaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((3-(hydroxysulfonyl)-7-(dimethylamino)naphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((4- methoxynaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((1-formylnapthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-(((1-carboxynaphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((1-amino-4- (hydroxysulfonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-(naphthalen-2-yl)aminophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,
1-(((3-aminonaphthalen-2-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-fluoro-4- (carboxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-(carboxymethyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,

1-((2-methoxy-4-(carboxymethyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- hydroxymethylphenxoy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(hydroxymethyl)-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-di(hydroxymethyl)-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-4-(hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((4-mercaptophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-(((2-carboxyindol-5-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((3-carboxyindol-5-yl) oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((indol-4- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((indol- 5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- (benzoxazol-2-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-methylquinolin-8-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((5,7-dibromoquinolin-8-yl)oxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-(((5,7-diiodoquinolin-8-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((5- nitroquinolin-8-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((quinolin-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((5-(hydroxysulfonyl)-7-iodoquinolin-8-yl)oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,
1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-carboxy-2,5,7,8-tetramethyl-2,3-dihydro-1-benzopyran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-oxo-3- chloro-4-methyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((2-oxo-3-(diethylamino)methyl)-4- methyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((2-oxo-6-methoxy-2*H*-1-benzopyran-7-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((2-oxo-2 *H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-formyl-6-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-formyl-6-iodophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-ethoxy-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4-formylphenox)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((2,4-dichloro-6-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2,4-dinitro-6-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-dinitro-6- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine:
1- ((2,4-dinitro-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2,5-dinitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((2-nitro-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2,4-dinitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-nitro-4-formyl-6-methoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-nitro-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,6-dinitro-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-nitro-4-(carboxymethyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,6- dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((3-methoxy-5-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-(1-methyl-1-phenylethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-(ethylamino)-4-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((2- acetylnaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-(carboxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-(carboxymethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-(((benzotriazol-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((quinolin-2-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2,6-dimethoxy-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3,4-dimethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,4,6-tri(*t*-butyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,6-dimethoxy- 4-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-trifluoromethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-methyl-5-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((4-(4-cyanophenyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-nitro-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-methylphenox) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- (methoxycarbonyl)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((carbazol-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-(((2-oxo-1,3-benzothiol-2-on-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-phenyl-4- oxo-4*H*-1-benzopyran-3-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-(((2-oxo-4-methyl-2*H*-1-benzopyran-7-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-nitrophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-carboxy-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-5-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((2-phenyl-4-oxo-2,3-dihydro-4*H*-1-benzopyran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((quinolin-6-yl) oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3- diaminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((4-(hydroxysulfonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((fluorenon-9-on-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((5,6,7,8- tetrahydronaphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4,6-tribromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2,6-dibromo-4-cyanophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-fluorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,3,5,6- tetrafluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2,6-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,3-dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2,3,6-trichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-chloro-4,5-dimethylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,5-dichlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-chloro-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(methylcarbonyl)aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-isopropoxyphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine,
1-((2-(benzyloxy)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-ethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- phenylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-(ethaxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-acetylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-(ethylcarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-(*t*-butyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-(1-methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,3-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2,3,5-trimethylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2,3,6-trimethylphenxoy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-dimethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,4,6- trimethoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- methyl-5-isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,5-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,5-dimethyl-4-(diethylamino)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(*t*- butyl)-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-prop-3-enyl-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-prop-2-enylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-ethylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-*n*- propylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((3-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,5-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-chloro-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((3,5-dichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-iodophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((3-(phenylamino)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((3-(diethylamino)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-phenylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-((3-acetylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((3-trifluoromethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-*t*- butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((3-methyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,4-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-*t*-butyl-5-methylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((2-isopropyl-5-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-ethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,6-dimethyl-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2, 6-dibromo-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-bromo-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-methyl-4-chlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-isopropyl-4-chloro-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((4-(methylcarbonyl)aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-ethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((4-propoxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl) piperazine,
1-((4-*n*-butoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-*n*- hexoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((4-*n*-heptoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(propoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-(ethylcarbonyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((4-(1,1,3,3-tetramethylbutyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(1,1- dimethylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-(1-methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-methoxy-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((2-acetyl-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(*t*-butyl)-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-(ethylamino)-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-(methoxycarbonyl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-ethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-*n*- propylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-carboxy-4,6-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((2-carboxy-4,6-dichlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-((2-carboxy-4,6-diiodophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-6- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-carboxy-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-5-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-carboxy-5-methoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-carboxy-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- carboxy-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-carboxy-4-iodophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-carboxy-4-methoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,3,4- trichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,3,4,5,6-pentachlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4,5-trichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-methoxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-((3-(methoxycarbonyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- (ethoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,6-dimethyl-4-bromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3,5-dimethyl-4-bromophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-methyl-4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-isopropyl-4-chloro-5-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((4-ethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((2-(t-butyl)-4-methylphenoxy)methyl)carbonyl-4- (4- chlorobenzyl)piperazine;

1-((3-formyl-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-prop-3- enylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- (1-phenyethyl)-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((4-(ethoxycarbonyl)methylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)puperazine,

1-((4-trifluoromethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-fluoro-4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- ((2-fluoro-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((7-methoxynaphthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-benzyloxy-4-cyanophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,

1-((2-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-bromo-3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((3,5-dimethoxy-4-bromophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,

1-((2,6-dibromo-3,5-dimethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((3-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1- ((2-methyl-3-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2-nitro-3-carboxy-6-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-cyanophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-5- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- nitro-5-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((3-(carboxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,

1-((2-methoxy-5-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,

1-((4-(dimethylamino)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(2- (dimethylamino)ethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((naphthalen-1-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-(((5-aminonaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-nitro-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2, 6-di(*t*-butyl)-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((3-carboxy-4-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine,
1-((2-methyl-5-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-nitro-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(benzyloxy)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- (aminocarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,5-di(trifluoromethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4-dibromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,6-dibromo-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,4-dichlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((3,5-dimethyl-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3,5-dicarboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-chloro-4-carboxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2,6-dichloro-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- (((2-carboxyquinolin-4-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,6-dimethyl-4-formylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2,6-di(*t*-butyl)-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-amino-5-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-di(*t*-butyl)-4-(hydroxymethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((4-carboxyquinolin-2- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-nitro- 4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((3-ethyl-4-chloro-5-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3,5-di(methoxycarbonyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,

1-((2-(morpholin-4-yl)methyl-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine
1- ((2-methoxy-4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-trifluoromethylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-methylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-methyl-4-acetylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-(dimethylamino) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- methyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3,5-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-phenylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((4-(ethoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-acetylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4- benzylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-4-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3-carboxynaphthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-(hydroxymethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((quinolin-8-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-aminophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- (aminocarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(cyclohexyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((quinolin-6-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,4-dichloro-3-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,5-dimethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-bromophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3- (methylcarbonyl)aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine,
1-((3-trifluoromethylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((4-bromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((2-formylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-((2-methoxy-5-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((tropinon-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-5- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-nitro-5-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,

1-((3-formyl-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-carboxy-5-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-amino-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-amino-3- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((2-nitro-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dichloro-4-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine,
1-((3-fluoro-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3-difluoro-6- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- chloro-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-nitro-4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-bromo-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-chlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine,
1-((3,4-dichlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,5-dichlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((3,4,5- trimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1- ((4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,5-dimethyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-methoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine,
1-((4-(methoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((4-t-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-isopropylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine,
1-(((naphthalen-2-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((6-bromonaphthalen-2- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- (hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-methoxy-5-(hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-(((1,3-benzodioxolan-5-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethyl-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2- methoxy-4-(amino)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3-(aminocarbonyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-(methoxycarbonyl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(4- phenylcarbonyl)-4-fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

1-((2-(1-methyl)cyclohexyl-2,4- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((2-(benzyloxycarbonyl)phenoxy)methyl)carbonyl-4-(4- fluorobenzyl)piperazine;

1-((2-(4-(methyl)phenylcarbonyl)-5- methoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1- ((2-phenylcarbonyl-5-octoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine;

1-((4-octylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine;

1-((2-(2-(carboxy)phenylcarbonyl-5-di(*n*-butyl) aminophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2- phenylcarbonyl-5-methoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine,

1-((2-methoxy-4-(3-hydroxyprop-2-enyl)phenoxy)methyl) carbonyl-4-(4-fluorobenzyl)piperazine;

1-(((3- (phenylaminocarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-(((6-(phenylcarbonyl)naphthalen-2-yl) oxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2-((2- phenylethyl)carbonyl)phenaxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((4-((4-fluorophenyl)carbonyl)phenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine

1-((2-(phenylamino)carbonylphenoxy) methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2- phenylcarbonylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2-phenylcarbonyl-4-chloro-5-methylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((4-(4-chlorophenyl)carbonylphenoxy) methyl)carbonyl-4-(4-fluorobenzyl)piperazine,

1-((4- benzylcarbonyl)phenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2-phenylcarbonyl-4-methylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine,

1-((4-(2-methylcarbonylethyl)phenoxy) methyl)carbonyl-4-(4-fluorobenzyl)piperazine,

1-((4- phenylcarbonylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine, and 1-((3-phenylcarbonylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine;

D. In a similar manner the following compounds of formula (Ia) or (Ib) were made:

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 0.86-1 02 (m, 3H), 1 04-1.36 (m, 3H), 2.16 (m, 1H), 2 62 (m, 1H), 2.94 (m, 1H), 3.08 (m, 0.5H), 3.42 (m, 1H), 3.58 (m, 1H), 3.76 (s, 3H), 3.98 (m, 1H), 4.40 (s, 0.5H), 4 82 (m, 1.5H), 5.02 (m, 0.5H), 6 98 (s, 1H), 7 14 (m, 2H), 7.38 (m, 2H), 7 56 (m, 1H), 7.62 (s, 1H)

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester; ^{1}H NMR (400 MHz, $CDCl_3$).δ/ppm = 0 90 (m, 3H), 1 30 (m, 3H), 2 25 (d, 1H), 2.68 (d, 1H), 3.00 (m, 1H), 3.20 (m, 1H), 3 40 (m, 1H), 3.50 (m, 2H), 3 62 (s, 2H), 3 68 (s, 3H), 4.65 (m, 3H), 6.80 (m, 1H), 7 00 (t, 2H), 7.30 (m, 4H).

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester, ^{1}H NMR (400 MHz, $CDCl_3$).δ/ppm = 1.30 (m, 3H), 2 00 (m, 1H), 2.10 (m, 1H), 2.60 (d, 1H), 2 80 (m, 1H), 3.45 (m, 2H), 3.60 (m, 2H), 3.62 (s, 3H), 4 30 (m, 1H), 4.65 (m, 2H), 4.75 (d, 2H), 6.78 (d, 1H), 7 00 (t, 2H), 7 30 (m, 4H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester; ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 0 76-0.98 (m, 3H), 1.08-1.30 (m, 3H), 2.16 (m, 1H), 2.62 (m, 1H), 2.94 (m, 1H), 3.08 (m, 0 5H), 3 58 (m, 3H), 3 73 (s, 3H), 4 00 (m, 1H), 4.40 (s, 0.5H), 4.88 (m, 1 5H), 5.08 (m, 0.5H), 6.96 (m, 1H), 7 14 (m, 2H), 7.36 (m, 2H), 7 66 (m, 1H), 7 84 (m, 1H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm = 0.76-0.97 (m, 3H), 1.08-1.32 (m, 3H), 2.16 (m, 1H), 2.62 (m, 1H), 2.94 (m, 1H), 3.08 (m, 1H), 3.40 (m, 1 5H), 3 58 (m, 1H), 3.73 (s, 3H), 3.87 (s, 3H), 4 00 (m, 1H), 4.40 (s, 0 5H), 4 92 (m, 1.5H), 5 08 (m, 0 5H), 6.68 (m, 1H), 7.14 (m, 2H), 7 36 (m, 2H), 7.86 (s, 1H)

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester, ^{1}H NMR (500 MHz, DMSO-d_6):δ/ppm = 0.90 (m, 3H), 1 25 (m, 3H), 2 23 (m, 1H), 2 75 (m, 2H), 2.94 (m, 1H), 3.35 (m, 1H), 3.45 (m, 1H), 3.63 (m, 1H), 3 77 (s, 3H), 3 92

(s, 3H), 4.31 (s, 1H), 4.92 (m, 2H), 6 81 (s, 1H), 7.12 (m, 2H), 7.37 (m, 2H), 7.72 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid methyl ester; ^{1}H NMR (400MHz, $CDCl_3$):δ/ppm = 0.78-0.98(m, 3H), 1.18-1.36 (m, 3H), 2 22 (m, 1H), 2.38 (s, 3H), 2.66 (m, 1H), 3.00 (m, 1H), 3.10-4.20 (m, 4H), 3.86 (s, 3H), 4 24-4 86 (m, 3H), 6 94-7.02 (m, 3H), 7.29 (m, 2H), 7.81 (s, 1H)

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester, ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 0.91 (d, 3H), 1.29 (d, 3H), 2 24 (d, 1H), 2 69 (dd, 1H), 3 02 (br, 1H), 3 41 (d, 1H), 3 47-3.71 (m, 2H), 3 87 (s, 3H), 4 10-4.22 (m, 1H), 4 60-4.86 (m, 3H), 7.00 (dd, 2H), 7 18 (br, 1H), 7.30 (dd, 2H), 7 91 (s, 1H)

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid methyl ester, ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 1 00 (m, 3H), 1.30 (m, 3H), 2 25 (d, 1H), 2.70 (dd, 1H), 3.05 (m, 1H), 3.20 (m, 1H), 3.50 (m, 2H), 3 68 (m, 1H), 3.95 (s, 3H), 4.20 (m, 1H), 4 80 (m, 2H), 7.00 (t, 2H), 7 30 (m, 3H), 7.90 (s, 1H)

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid methyl ester, ^{1}H NMR (400 MHz, DMSO-d_6)·δ/ppm = 0 62 (m - rotamer, 1 25H), 0.73 (t - rotamer, 3.5H), 0.85 (m - rotamer, 1 25H), 1.23 (m, 1H), 1 37 (m, 1H), 1 55 (m, 1H), 1 70 (m, 1H), 1.83 (m, 1H), 2.26 (t, 1H), 2 55 (d, 1H), 2.75 (d – rotamer, 1H), 3.45 (dd, 1H), 3.47 (t, 1H), 3.60 (m, 1H), 3.78 (s, 3H), 4 20 (d, 1H), 4 90 (m – rotamer, 2H), 6.99 (d, 1H), 7.13 (t, 2H), 7 35 (t, 2H), 7.55 (dd, 1H), 7 64 (d, 1H).

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester; . ^{1}H NMR (400 MHz, DMSO-d_6)·δ/ppm = 0 60-0 90 (m, 6H), 1.06-1 60 (m, 3H), 1.62-1.82 (m, 1.5H), 2 16 (m, 1H), 2 60 (m, 2H), 2.88 (m, 1H), 3 46 (m, 1H), 3 60 (m, 1.5H), 3 76 (s, 3H), 3.85 (s, 3H), 4.22 (m, 1H), 4 92 (m, 1H), 5 12 (m, 1H), 6 68 (m, 1H), 7.12 (m, 2H), 7 34 (m, 2H), 7.86 (s, 1H)

5-bromo-2-[2-[(2*R*)-4-[(5-chloro-2-thienyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester, ^{1}H NMR (400 MHz, $CDCl_3$).δ/ppm = 1 30 (m, 3H), 2 05 (m, 1H), 2.15 (m, 1H), 2 75 (m, 1H), 2.90 (m, 1H), 3.05 (m, 1H), 3.45 (m, 1H), 3 60 (m, 2H), 3.65 (s, 2H), 3.70 (s, 3H), 4 35 (m, 1H), 4.68 (m, 2H), 6 65 (d, 1H), 6 72 (d, 1H), 6.80 (dd, 1H), 7.35 (m, 2H)

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid, ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 0 73-0.88 (m, 3H), 1.12-1 25 (m, 3H), 2.05-2 20 (m, 1H), 2 65 (m, 1H), 2 90 (m, 1H), 3 08 (m, 0 5H), 3 50 (m, 3H), 3 97 (m, 0.5H), 4.40 (m, 1H), 4.75 (m, 1 5H), 4.94 (m, 0.5H), 6.93 (m, 1H), 7.12 (m, 3H), 7.34 (m, 3H), 7.57 (m, 1H).

5-chloro-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid; . ^{1}H NMR (400 MHz, DMSO-d_6 + TFA): δ/ppm = 1 16 (d, 3H), 1 32 (d, 3H), 2 76-3.50 (m, 5H), 4 24-4 52 (m, 3H), 4 60-5.00 (m, 3H), 6.50 (m, 1H), 7.23 (m, 2H), 7.30 (m, 1H), 7 54 (m, 2H), 7.67 (m, 1H), 9 50 (br, 1H).

EXAMPLE 3

Compounds of Formula (Ia) and Formula (Ib)

A To a solution of 1- ((3,4,5-trimethoxyphenoxy)methyl)carbonylpiperazine (0 22 g, 0.70 mmol) in 1% acetic acid in methanol (6 mL) was added 4-cyanobenzaldehyde (0 33 g, 2.5 mmol) and sodium cyanoborohydride (0 093 g, 1 4 mmol). The resultant mixture was stirred at ambient temperature for 1 5 hours and the mixture was then concentrated of volatiles *in vacuo*. Residue was taken up in ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution, water, and then brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil Purification by flash column chromatography on silica gel afforded 0.21 g of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-cyanobenzyl)piperazine, a compound of formula (Ib), as a clear oil NMR ($CDCl_3$) 7 6 (d, 2), 7.4 (d, 2), 6.2 (s, 2), 4 6 (s, 2), 3.8 (s, 6), 3.75 (s, 3), 3.6 (m, 4), 3 5 (s, 2), 2.2 (m, 4) ppm

B. In a similar manner, other compounds of formula (Ib) were made:

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(3,4-dimethoxybenzyl)piperazine,
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-methoxybenzyl) piperazine,
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- chlorobenzyl)piperazine,
1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(3-trifluoromethylbenzyl)piperazine;
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(2,3-dimethyl-4-methoxybenzyl) piperazine;
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- phenoxybenzyl)piperazine,

1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(4-(dimethylamino)benzyl)piperazine;
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-(methylthio)benzyl)piperazine;
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-methoxy3-methylbenzyl)piperazine,
1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(2-chlorobenzyl)piperazine;
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(3-nitrobenzyl)piperazine;
1- ((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-hydroxybenzyl)piperazine;
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3,5-dibromo-4-hydroxybenzyl)piperazine,
1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(2-fluorobenzyl)piperazine;
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (m, 2), 6 2 (s, 2), 4.6 (s, 2) , 3.9 (m, 9), 3 6 (m, 4), 3 4 (s, 2), 2 4 (m, 4) ppm;
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-bromobenzyl)piperazine, NMR ($CDCl_3$) 7 4 (d, 2), 7.2 (d, 2), 6 2 (s, 2), 4 6 (s, 2) , 3.85 (s, 6), 3 75 (s, 3), 3.6 (m, 4), 3.4 (s, 2), 2.4 (m, 4) ppm,
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2-bromobenzyl) piperazine,
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- fluorobenzyl)piperazine;
1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(3-bromobenzyl)piperazine,
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(3-cyanobenzyl)piperazine;
1- ((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2,4-difluorobenzyl) piperazine;
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2,3- difluorobenzyl)piperazine,
1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(3,4-difluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3-7.0 (m, 3), 6.2 (s, 2), 4.6 (s, 2), 3.85 (s, 6), 3.75 (s, 3), 3.6 (m, 4), 3.5 (s, 2), 2.4 (m, 4) ppm;
1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-4-(2,6-difluorobenzyl)piperazine;
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (m, 4), 6.2 (s, 2), 4 6 (s, 2), 3.85 (s, 6), 3.75 (s, 3), 3.6 (m, 4), 3.5 (s, 2), 2 4 (m, 4) ppm;
1-((3,4, 5-trimethoxyphenoxy)methyl)carbonyl-4-(3-chloro-4-fluorobenzyl)piperazine;
1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-trifluoromethylbenzyl)piperazine;
1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-4-(4-nitrobenzyl)piperazine;
1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine,

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2,5-difluorobenzyl) piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- nitro-4-hydroxybenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 2 (m, 4), 7.0 (t, 2), 6 8 (d, 2). 4.6 (s, 2), 3.6 (m, 4), 3.4 (s, 2), 2 4 (m, 4) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (m, 6), 6 8 (d, 2), 4.6 (s, 2), 3.6 (m, 4), 3.5 (s, 2), 2 4 (m, 4) ppm;

1- ((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3-(benzyloxy)benzyl) piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-4-(3,4,5- trimethoxybenzyl)piperazine;

C In a similar manner, the following compounds of formula (Ia) were made·

(3*S*)-1-((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4- fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7 0 (t, 2), 6.9 (d, 2), 4.6 (s, 2), 4.0 (m, 2), 3.7 (m, 1), 3.4-2.9 (m, 3), 2 7 (m, 1), 2.5 (m, 1), 2.1 (m, 1), 1.1 (m, 3) ppm;

(3*R*)-1- ((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7 0 (t, 2), 6.9 (d, 2), 4 6 (s, 2), 4.0 (m, 2), 3.7 (m, 1), 3.4-2 9 (m, 3), 3.2 (m, 1), 3.0 (m, 1), 2. 7 (m, 1), 2.5 (m, 1), 2.1 (m, 1), 1.1 (m, 3) ppm;

1-((4- chlorophenoxy)methyl)carbonyl-3-(2-((((4-chlorophenoxy)methyl)carbonyl) oxy)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy) methyl)carbonyl-2-hydroxyethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt,

1-((4-chlorophenoxy)methyl)carbonyl-2-(2- ((2-methylpropyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 1 (m, 4), 6 9 (t, 2), 6 7 (d, 2), 4.6 (s, 2), 4 4 (d, 1), 3 6 (d, 1), 3.3 (m, 3), 2.7-2 3 (m, 6), 2 0-1.7 (m, 5) , 0.8 (t, 6) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((4- fluorobenzyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine, hydrochloride salt,

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2-hydroxyethyl) amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy) methyl)carbonyl-2-(2-((methyl)amino)ethyl)4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-3-(2-((4-fluorobenzyl)amino) ethyl)-4-(4-fluorobenzyl)piperazine, hydrochloride salt;

1-((4- chlorophenoxy)methyl)carbonyl-3-(2-((methyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-3- (2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-((2-methylpropyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((ethyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (d, 2), 6 9 (t, 1), 6.4 (br s, 2), 5.0-4.6 (m, 3), 4 0 (m, 3), 3.7-3.2 (m, 4), 3.0-2. 7 (m, 3) , 2.2 (m, 1), 1.3 (m, 6), 1.0 (br d, 3) ppm,

(*trans*)-1-((4-chloro-2-(((diethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.5 (d, 1), 7 3 (m, 2), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 3), 4.2 (m, 1), 3 6-3.4 (m, 4), 3.2 (m, 1), 3 0 (m, 1), 2 7 (dd, 1), 2.6 (q, 2), 2.2 (d, 1), 1.3 (m, 3), 1.0 (m, 9) ppm,

(*trans*)-1-((4- chloro-2-(((cyclopropyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7 0 (d, 2), 6 8 (t, 1), 4 8-4 0 (m, 6), 3 7-3 2 (m, 3), 3.0 (br s, 1), 2 7 (d, 1), 2.2 (m, 2), 1 3 (m, 3), 0.9 (m, 3), 0 5 (m, 4) ppm,

(*trans*)-1-((4-chloro-2-(((dimethyl)amino)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7.1 (dd, 1), 7.0 (t, 2), 6 8 (d, 1), 4.7 (m, 3), 4.1 (m, 1), 3.6-3.4 (m, 4), 3.0 (br s, 1), 2 7 (dd, 1), 2 2 (m, 8) , 1.3 (m, 3), 0 9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(((methyl)amino)methyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7.1 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 2), 4 1 (m, 1), 3 7-3 4 (m, 5), 3.0 (br s, 1), 2 7 (dd, 1), 2 4 (s, 3) , 2 2 (m, 2), 1.3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-((amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (m, 4), 7.1 (dd, 1), 7 0 (t, 2), 6 7 (d, 1), 4.7 (m, 2), 3.8 (d, 1), 3.5 (m, 4), 3.0 (br s, 1), 2.7 (dt, 1), 2.2 (d, 1), 1 3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((4-methylpiperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 1 (dd, 1), 7 0 (t, 2), 6.8 (d, 1), 4.7 (m, 4), 4 2 (m, 1), 3.8 (m, 1), 3.6-3 0 (m, 8), 2 9 (t, 1), 2 7 (m, 1), 2. 5-2.2 (m, 6), 1.3 (m, 3), 0.9 (m, 3) ppm,

(*trans*)-1-((4- chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 7 9 (m, 3), 7.7 (s, 2). 7.4 (t, 1), 7 2 (m, 2), 5.4 (d, 1), 5 0 (m, 2), 4 3 (m, 4), 3 6- 3 1 (m, 12), 2.8 (m, 1), 1 5-1 0 (m, 6) ppm;

(*trans*)-1- ((4-chloro-2-(((2-hydroxyethyl)amino)methyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7.1 (dd, 1), 7 0 (t, 2), 6 7 (d, 1), 4.7 (m, 2), 4.2-3.4 (m, 6), 3.0 (br s, 2), 2.7 (m, 4), 2.2 (d, 2), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((morpholin-4-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 3), 7 1 (dd, 1), 7.0 (t, 2), 6 7 (d, 1), 4.7 (m, 2), 4.1-3 4 (m, 11), 3.0 (br s, 1), 2 7 (dd, 1), 2.5 (t, 4), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2- (ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7 3 (m, 3), 7.2 (dd, 1), 7 0 (t, 2), 6.8 (m, 1), 4.7 (m, 2), 4.1 (m, 1), 3 8 (s, 2), 3 6 (m, 1), 3.5 (q, 2) , 3.0 (m, 1), 2 7 (m, 3), 2 6 (q, 2), 1.3 (m, 3), 1.1 (t, 3), 1.0 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-((ethyl)(1-methylbutyl) aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR (DMSO-d_6) 7 9 (m, 1), 7 7 (m, 2), 7.5 (m, 1), 7 2 (m, 3), 5.1 (m, 1), 4 6 (d, 1), 4.3 (m, 2), 3 7-2 8 (m, 6), 2. 5 (s, 2), 1.5- 1.2 (m, 19), 0 8 (s, 3) ppm,

(*trans*)-1-((4-chloro-2-(benzylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 7), 7.0 (t, 2), 6 7 (d, 1), 6.6 (m, 2), 4 7 (d, 2), 4 4 (s, 2), 4.2-3.0 (m, 8), 2.6 (dd, 1), 2.2 (d, 1), 1 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 7.9 (m, 2), 7.3 (t, 2), 7.1 (m, 1), 6 9 (d, 2), 5.2 (d, 1), 4.9 (m, 2), 4 6 (m, 1), 4.5-3 2 (m, 6), 2 8 (t, 1), 2.5 (s, 1) , 1.7-1 2 (m, 9), 0.9 (d, 6) ppm,

(*trans*)-1-((4- chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7. 3 (m, 3) 7 1 (dd, 1), 7.0 (t, 2), 6.8 (br d, 1), 4.7 (m, 2), 3.8 (s, 2), 3 6 (m, 1), 3 5 (q, 2), 3 0 (m, 2), 2.7 (dd, 1), 2.4 (m, 3), 2 2 (d, 1), 1.3 (m, 3), 0.9 (m, 4), 0 4 (m, 2), 0 1 (m, 2) ppm,

(*trans*)-1-((4-chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 7.8 (m, 2) , 7.4 (m, 8), 7 2 (m, 2), 5.4 (d, 1), 5.0 (m, 2), 4.7 (m, 1), 4 5 (s, 2), 4 3 (m, 2), 3.9-3.4 (m, 4), 1.4 (m, 3), 1 2 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(1-((methyl)(ethyl)amino)ethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 4 (s, 1), 7.3 (m,

2), 7.1 (dd, 1), 7 0 (t, 2), 6.8 (br d, 1), 4 6 (br s, 3), 4 0 (m, 2), 3 6 (d, 1), 3 4 (d, 1), 3.0 (m, 1), 2 7 (dd, 1), 2.5 (d q, 1), 2.4 (d q, 1), 2.2 (s, 3), 1.3 (m, 6), 1 0 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(1-(dimethylamino)ethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (CD_3OD) 7.6 (m, 3), 7.5 (d, 1), 7 3 (m, 3), 5.1 (m, 3) , 4 4 (m, 2), 3 8 (dd, 2), 3 6 (m, 1), 3 4 (m, 1), 3 0 (m, 1), 2 6 (m, 7), 1 6 (m, 6), 1 3 (m, 3) ppm;

(2R)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 3), 7 0 (t, 2), 6.8 (d, 1), 4.7 (m, 2), 4 4 (m, 1), 3 5 (m, 10), 3 0 (m, 1), 2.8 (m, 1), 2 6 (m, 2), 1 4 (m, 12), 1 2 (m, 3) ppm;

(*trans*)- 1-((4-chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 7.8 (m, 2), 7,6 (s, 1), 7 5 (m, 1), 7 3 (t, 2), 7 2 (m, 1), 5 4 (d, 1), 5.0 (m, 2), 4 7 (m, 1), 4 3 (m, 6), 4 0 (m, 2), 3 8-3 1 (m, 8) , 2 9 (m, 1), 1.4 (m, 12), 1.2 (m, 3) ppm,

1-((4-chloro-2-(morpholin-4-ylmethyl)phenoxy)methyl) carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11. 5 (br d, 1), 10.6 (m, 1), 7 7 (m, 2), 7 6 (s, 1), 7.5 (dd, 1), 7 3 (t, 2), 7 2 (d, 1), 5.2 (q d, 2), 4 7 (m, 1), 4 4 (m, 4), 3.9-3.7 (m, 4), 3.5 (m, 1), 3 4 (m, 4), 3 0 (m, 4), 2.8 (m, 1), 1.5 (d, 1.5), 1.3 (d, 1 5) ppm.

5-chloro-4-(dimethylamino)-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm = 1 10-1.30 (m, 6H), 2 82 (s, 6H), 3 00 (m, 1H), 3 21 (m, 0.5), 3.40 (m, 1H), 3.58-3 70 (m, 2H), 4.20-4 40 (m, 3H), 4.70 (m, 0.5H), 4 90-5.10 (m, 2H), 6 62 (s, 1H), 7 30 (t, 2H), 7.60 (m, 2H), 7.68 (m, 1H).

EXAMPLE 4

Compounds of Formula (Ia)

A. To a solution of (2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((hydroxy) methyl)piperazine (0.17 g, 0.42 mmol) in CH_2Cl_2 (50 mL) at 0°C was added triethylamine (excess) and methane sulfonyl chloride (0 050 mL, 0 5 mmol) The resultant mixture was stirred at 0°C until consumption of alcohol was observed by TLC analysis The mixture was concentrated of volatiles *in vacuo* Residue was taken up in anhydrous DMF (5 mL) and K_2CO_3 (excess) added, followed by tetrazole (0.050 g, 0.71 mmol) The resulting mixture

was stirred at ambient temperature for 3 days and filtered The filtrate was concentrated *in vacuo* and the residue taken up in ethyl acetate. This was washed with water then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography on silica gel afforded 25 mg of (2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl) piperazine as a white solid NMR ($CDCl_3$) 7 3 (m, 5), 7.0 (m, 4), 4.8-4.1 (m, 5), 3 8 (m, 3), 3 2 (m, 2), 2.8 (dd, 1), 2.5 (dd, 1), 1 4 (d, 3) ppm, MS (ESI) 458

B In a similar manner, the following compounds of formula (Ia) were made.

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl)piperazine, NMR ($CDCl_3$) 7.9 (s, 1), 7.3(m, 5), 6 9 (m, 4), 4.7 (m, 3), 4.4-3.4 (m, 5), 3.1-2.7 (m, 2), 2.4 (t, 1), 2 0 (d, 1), 1.2 (m, 3) ppm;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7.0 (t, 2), 6 8 (d, 2), 4.7-4 1 (m, 5), 3 9-3.4 (m, 9), 3 2-2 7 (m, 3), 2.3 (m, 2), 2.0 (m, 1), 1 2 (m, 3) ppm;

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1-yl)methyl)piperazine;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)-5-((diethylamino)methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6 9 (d, 2), 4.7 (m, 3) , 3 9-3 4 (m, 4), 2 8-2 3 (m, 7), 1.2 (m, 3), 0.9 (t, 6) ppm,

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-(((ethyl)amino)methyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6.9 (d, 2), 4 7 (m, 3), 4 2-3 4 (m, 5), 2 8-2 3 (m, 6), 1.3-1.0 (m, 6) ppm,

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((4-methylpiperazin-1-yl)methyl)piperazine, NMR ($CDCl_3$) 7. 3 (m, 4), 7 0 (t, 2), 6.9 (d, 2), 4 7 (m, 3), 3 9-3 4 (m, 4), 2 8-2 2 (m, 14), 1.2 (m, 3) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-4-(4- fluorobenzyl)-3-(2-(4-(*t*-butoxycarbonyl)piperazin-1-yl)ethyl) piperazine, hydrochloride salt

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((dimethylamino)methyl)piperazine

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (m, 4), 4 6 (m, 4), 4.2-3.2 (m, 4), 2.6-2.2 (m, 4), 1 2 (m, 3) ppm;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-((((cyclopropyl)methyl)amino)methyl)piperazine,

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-(((2-hydroxyethyl)thio)methyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6.8 (d, 2), 4 7 (m, 3), 4.1-3 5 (m, 5), 3.1-2 3 (m, 8), 1.3 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-(imidazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine, NMR (DMSO-d_6) 11.3 (m, 1), 9 4 (s, 1), 7 9 (s, 3), 7.6 (s, 2), 7 4 (m, 1), 7 3 (m, 3), 7.1 (m, 1), 5 4 (m, 2), 4 9 (m, 1), 4.2 (m, 2), 3 8-3.2 (m, 6), 2 7 (m, 1), 1.4-1.2 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.6 (s, 1), 7 3 (m, 2), 7.2 (dd, 1), 7.0 (m, 5), 6 8 (d, 1), 5.8 (q, 1), 4.6 (m, 3), 4.2 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3 0 (m, 1), 2. 7 (dd, 1), 2.2 (dd, 1), 2.0 (br s, 1), 1 8 (dd, 3), 1 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(triazol-1- ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 8 4 (s, 1), 7.9 (s, 1), 7.3 (m, 3), 7.0 (t, 2), 6.8 (d, 1), 5.4 (s, 2), 4.6 (m, 3), 4.2 (m, 1), 3 5 (q, 2), 3.2 (m, 1), 3 0 (m, 1), 2.9 (dd, 1), 2.2 (dd, 1), 1.3 (m, 3), 0.9 (m, 3) ppm, and

(*trans*)-1-((4-chloro-2-(tetrazol-1- ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 9 4 (s, 1), 7.4 (s, 1), 7.3 (m, 3), 7.0 (t, 2), 6 8 (d, 1), 5.6 (s, 2), 4 7 (m, 3), 4 2 (m, 1), 3.5 (q, 2), 3 2 (m, 1), 3. 0 (m, 1), 2.9 (dd, 1), 2.2 (dd, 1), 1.3 (m, 3), 0 9 (m, 3) ppm.

EXAMPLE 5

Compounds of Formula (Ia)

A To a solution of oxalyl chloride (0.62 g, 5 mmol) in CH_2Cl_2 (20 mL) at -50°C was added DMSO (0 85 g, 11 mmol, in solution of 5 mL of CH_2Cl_2) over 2 minutes. 4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine (1.85 g, 4 5 mmol, in solution of 5 mL of CH_2Cl_2) was added The resulting mixture was stirred at -50°C for 15 minutes, then triethylamine (2 3 g, 22 mmol) was added After 5 minutes at -50°C, the mixture was gradually warmed to ambient temperature At that time the mixture was diluted with CH_2Cl_2 and washed with water, then brine. The organic layer was

then dried over $MgSO_4$ and concentrated *in vacuo* to afford 1 7 g of 4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-((formyl)methyl)piperazine as a yellow oil; NMR ($CDCl_3$) 9 8 (d, 1) 7 3 (m, 4), 7.0 (m, 4), 4.6 (m, 3), 3 8-3 2 (m, 7), 2.7-2.2 (m, 4) ppm.

B In a similar manner, the following compounds of formula (Ia) were made

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-((acetyl)methyl)piperazine, hydrochloride salt; NMR ($CDCl_3$) 7 3 (m, 4), 6 9 (m, 4), 4.6 (m, 2), 3.8-3.3 (m, 7), 2. 4 (m, 4), 2 1 (d, 3) ppm; and

(2*R*,5*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-formylpiperazine.

EXAMPLE 6

Compounds of Formula (Ia)

A To a solution of 4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((formyl)methyl) piperazine (0.31 g, 0 77 mmol) in anhydrous THF (20 mL) was added methyl magnesium bromide (0 26 mL, 0.77 mmol, 3 0 M solution in ether). The resultant mixture was stirred overnight at ambient temperature At that time the mixture was poured into 5% aqueous NH_4Cl solution and extracted with two portions of ether The combined organic extracts were washed with brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography on silica gel afforded 0.29 g of 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxypropyl)piperazine, as a clear, colorless oil, which was converted to its hydrochloride salt; NMR ($CDCl_3$) 7 6 (m, 2), 7 2 (m, 4), 6.9 (m, 2), 4 7 (m, 2), 4 4-3.0 (m, 10), 2 4-1 4 (m, 2) 1.3-1 0 (m, 3) ppm.

B. In a similar manner, the following compounds of formula (Ia) were made:

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2-phenylethyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 9), 7.0 (t, 2), 6 8 (d, 2), 4.9 (m, 1), 4.8 (m, 2), 4 1 (m, 1), 3.8-3 3 (m, 6), 2 8 (m, 2), 2 2 (m, 1), 2 0 (m, 2) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxypentyl)piperazine, NMR ($CDCl_3$) 7 8 (m, 2), 7.3 (m, 4), 6.9 (d, 2), 4 8 (d, 2), 4.5-3.0 (m, 16) 2.2-1 2 (m, 8) , 0.9 (m, 3) ppm,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(2-hydroxybut-4-enyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 8 (d, 2), 5.7 (m, 1), 5 2

(dd, 1), 5.1 (t, 1), 4 6 (m, 2), 4.2-3 3 (m, 7), 2 9 (m, 2), 2.4 (m, 1), 1.9-1.5 (m, 2) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-hydroxyprop-2-enyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 10.1 (b s, 1), 7 6 (m, 2), 7 3 (d, 4), 6.9 (d, 2), 6 1 (m, 1), 5.9 (m, 1), 5.4 (m, 2), 4.8 (m, 2), 4.4 (m, 4), 3 7-3.1 (m, 5), 1.1 (m, 3) ppm;

(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxybutyl)piperazine, hydrochloride salt, NMR (DMSO-d_6) 10.3 (b s, 1), 7.6 (m, 2), 7 3 (m, 4), 6.9 (d, 2), 5 6 (m, 1), 4 9 (m, 2), 4.4 (m, 3), 3.9-3 1 (m, 5), 1.4 (m, 4), 1 1 (d, 3), 0. 8 (t, 3) ppm,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxybut-4-ynyl)piperazine,

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2-cyclohexylethyl) piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyethyl)piperazine hydrochloride salt, NMR (DMSO-d_6) 10.3 (b s, 1), 7 6 (m, 2), 7.3(m, 4), 6.9 (d, 2), 5.6 (b s, 1), 4 9 (m, 2), 4.6-4 0 (m, 6), 3.2 (m, 3), 1.2 (d, 3), 1.1 (d, 3) ppm;

(2*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl)piperazine, hydrochloride salt;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine,

(*trans*)-1-((4-chloro-2-(1- hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7 2-6.8 (m, 4), 5 1 (m, 1), 4.7 (m, 2), 4.2-3 0 (m, 9), 2.7 (dd, 1), 2 3 (d, 1), 1 5 (d, 3), 1.3 (br m, 3), 0 9 (br m, 3) ppm,

1-((4-chlorophenoxy)methyl) carbonyl-2-(1-hydroxyethyl)-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 2 (m, 4), 7.0 (m, 2), 6 8 (dd, 2), 4 7 (m, 3), 4 2 (m, 1), 3.8 (m, 1), 3 4 (s, 2), 3 2 (m, 1), 2.3 (dd, 1), 2 1 (m, 1), 1 1 (m, 3) ppm,

1-((4-chlorophenoxy)methyl)carbonyl-2-(2- hydroxypropyl)-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 7 6 (br s, 2), 7.3 (d, 4), 6 9 (q, 2), 4.9 (m, 3), 4 3 (m, 3), 3 9 (m, 3) , 3.3. (m, 2), 3 0 (m, 1), 2 2 (t, 1), 1.8 (m, 1), 1.5 (m, 1), 1. 1 (d, 1.5) , 1 0 (d, 1.5) ppm, and

1-((4-chlorophenoxy)methyl) carbonyl-2-(2-hydroxybut-3-enyl)-4-(4-fluorobenzyl)piperazine, NMR (DMSO- d_6) 7.6 (dt, 2), 7.3 (m, 4), 6.9 (t, 2), 5.8 (m, 1), 5.2 (dd, 1), 5 0 (dt, 2), 4 8 (dt, 1), 4.4 (m, 2), 3.9 (m, 1), 3.4 (m, 3), 3.0 (m, 3), 2.2 (m, 1) , 1 8 (m, 1), 1 6 (m, 1) ppm.

EXAMPLE 7

Compounds of Formula (Ia)

A To a solution of 4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2- phenylethyl)piperazine (0 051 g, 0.11 mmol) in anhydrous ether (5 mL) was added sodium hydride (0.006 g, 0 15 mmol). The resultant mixture was stirred at ambient temperature for 30 minutes, then methyl iodide (0 016 g, 0.11 mmol) was added. Once thin layer chromatography analysis showed complete consumption of 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxy-2-phenylethyl)piperazine had occurred, the mixture was poured into water and extracted with two portions of ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 0 046 g of 4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-methoxy-2-phenylethyl)piperazine as a yellow oil: NMR ($CDCl_3$) 7 3 (m, 9), 7.0 (m, 2), 6.9 (m, 2), 4.8 (m, 3), 4.2 (m, 2), 3.9-3.2 (m, 5), 3 1 (d, 2), 3 0 (s, 1), 2.9 (s, 1), 2.6 (m, 1), 2.4 (m, 1), 1.9 (m, 1) ppm.

B In a similar manner, other compounds of the invention were made.

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-((methoxy) methyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6.9 (d, 2), 4.8 (m, 3), 3.8-3 1 (m, 9), 3 0 (br s, 1), 2.7 (dd, 1), 2.3 (t, 1) , 1 2 (m, 3) ppm,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(2-(methoxy)ethyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4 7 (m, 3), 4 1 (m, 1), 3.7 (m, 1), 3.4-3 2 (m, 6), 2 8 (m, 3), 2.0 (m, 4) ppm;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) methylpiperazine-2-one,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonylpiperazine-2-one;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-((methoxy)methyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (dd, 2), 4 7 (d, 2), 3 9-3 3 (m, 11), 2 6 (m, 2), 2 2 (m, 1) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- (2-(methoxy)ethyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6.9 (dd, 2), 4.7 (d, 2), 3.8-3.3 (m, 11), 2.6 (m, 2), 2.2 (m, 1) , 1 8 (m, 2) ppm,

4-(4-fluorobenzyl)-1-(2-(4-chlorophenoxy)ethyl) piperazin-2-one; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 4.2 (t, 2), 3.8 (t, 2), 3.5 (m, 4), 3 2 (s, 2), 2 6 (t, 2) ppm,

4-(4-fluorobenzyl)-1-(2-(4-chlorophenoxy)ethyl)-3-((ethoxycarbonyl)methyl)piperazin-2-one, hydrochloride salt, NMR ($CDCl_3$) 7 2 (m, 2), 7 1 (m, 4), 6.8 (d, 2), 4.2 (m, 9), 3.5 (m, 5), 2.9 (br s, 1), 1.3 (t, 3) ppm;

(*trans*)-1-((4-chloro- 2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine, NMR ($CDCl_3$) 7.3 (m, 2), 7.0-6 8 (m, 5), 4 7 (br m, 2 5), 4.2 (br s, 0 5), 3.8 (s, 3), 3.6-3.2 (m, 4), 3 0 (br s, 1), 2.7 (m, 1), 2. 2 (d, 1), 1.2 (br m, 3), 1.9 (br m, 3) ppm; and

(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 2), 7 0-6 8 (m, 5), 4 7 (br m, 2.5), 4.2 (br s, 0.5), 3 8 (s, 3), 3.6-3.2 (m, 4), 3 0 (br s, 1), 2.7 (m, 1), 2.2 (d, 1), 1.2 (br m, 3), 1 9 (br m, 3) ppm.

EXAMPLE 8

Compounds of formula (Ia)

A. To a solution of 4-chlorobenzylisocyanate (0.59 g, 3 5 mmol) in anhydrous THF (15 mL) at 0°C was added 1-(4-chlorobenzyl) piperazine (0 74 g, 3.5 mmol) The resultant mixture was stirred at ambient temperature After 20 hours the mixture was concentrated of volatiles. The resulting solid was washed with ethyl acetate and dried *in vacuo* to afford 0 72 g of 1-(((4-chlorobenzyl)amino)carbonyl)-4-(4-chlorobenzyl)piperazine as a white solid; NMR ($CDCl_3$) 7 4 (m, 4), 7 3 (m, 2), 7.2 (m, 2), 4.4-4 1 (m, 6), 3 6 (m, 4), 3.0 (m, 2) ppm

B. In a similar manner, other compounds of formula (Ia) were made.

4-(4-fluorobenzyl)-1- ((4- chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl) piperazine; NMR ($CDCl_3$) 7 2 (m, 4), 7 0 (t, 2), 6.8 (dd, 2), 5 7 (br s, 1), 5 2 (m, 1), 5 0 (m, 1), 4 8-2.0 (m, 15) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- (*N'*-(ethoxycarbonylmethyl) ureido)methyl)piperazine, NMR (DMSO-d_6) 7 3 (m, 4), 7.1 (t, 2), 6.8 (d, 2), 6 5 (t, 2), 4 8 (m, 2), 4.1-1.8 (m, 15), 1 1 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.8 (br s, 1), 8 3 (s, 1), 7.3 (m, 2), 7.0 (m, 3), 6 8 (d, 1), 6.0 (br s, 1), 5 0 (m, 2), 4.8 (m, 2), 4 1 (m, 3), 3.6 (m, 3), 3 1 (m, 2), 2.7 (d, 1), 2.3 (d, 1), 0 9 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 9 8 (br m, 1), 9.4 (s, 1), 8.2 (s, 1), 7.6 (m, 2), 7.3 (m, 2), 7.0 (m, 2), 6.0 (br m, 2), 5.0 (m, 3), 4 3 (br m, 3), 4 0 (s, 2), 3.7-3.2 (m, 4), 2.8 (s, 3), 1.3 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-ethylureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 8 8 (s, 1), 8.4 (s, 1), 7.3 (m, 2), 7 0 (m, 2), 6.8 (m, 3), 4 7 (m, 2), 4 1 (m, 2), 3 6-3 3 (m, 4), 3. 0 (br s, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 5), 0.9 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 10.4 (br d, 1), 9.2 (s, 1), 9 1 (s, 1), 8.2 (s, 1), 8.1 (d, 1), 7.7 (m, 2), 7 3 (m, 3), 6.9 (m, 2), 5.0 (m, 2), 4.7 (m, 1) , 4.3 (m, 3), 3 8 (q, 1), 3.6 (m, 1), 3 4 (m, 1), 2 9 (t, 1), 1.4 (m, 3), 1.2 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(*N'*- (4-nitrophenyl)ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine, NMR ($CDCl_3$) 9.1 (s, 1), 8 4 (s, 1), 8.3 (s, 1), 8.2 (s, 1), 7.9 (d, 1), 7.8 (d, 1), 7 3 (m, 3), 7.0 (t, 2) , 6 8 (d, 1), 6.7 (m, 1), 4.7 (m, 2), 3 6 (m, 4), 3.1 (m, 1), 2 8 (m, 1), 2.3 (d, 1), 1.4 (m, 3), 1 0 (m, 3) ppm;

(*trans*)-1- ((4-chloro-2-(*N'*-(4-methylphenyl)ureido)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10 5 (br d, 1), 9.6 (s, 1), 8.5 (d, 1), 8.2 (s, 1), 7.8 (m, 2), 7.3 (m, 4), 7. 1 (d, 2), 6 9 (s, 1), 5 0 (m, 2), 4.3 (m, 3), 3.9 (s, 1), 3.6 (m, 1) , 3 4 (m, 1), 2 8 (dd, 1), 2 2 (s, 3), 1.4 (m, 3), 1.2 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.0 (s, 1), 8 4 (s, 1), 7 3 (m, 8), 7.0 (t, 2), 6.8 (q, 2), 5.6 (t, 1), 4 6 (m, 4), 3.6 (m, 3), 3 0 (m, 1), 2 7 (m, 1), 2 2 (m, 2), 1. 3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 8 (d, 1), 5 6 (m, 1), 5.4 (br

d, 1) 4.7 (m, 2), 3.5 (q, 2), 3 2 (m, 4), 3 0 (m, 1), 2.7 (m, 4), 2 2 (d, 1), 1.4 (d, 3), 1.3 (m, 9), 0.9 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-(oxazol-2-ylaminomethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7.3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4 7 (m, 3), 4.4 (s, 2), 4 3 (t, 2), 3.9 (m, 1), 3 8 (t, 2), 3 5 (q, 2), 3 3 (m, 1), 3 0 (m, 1), 2.7 (dd, 1), 2 2 (d, 1), 1 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(ureido)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7 3 (m, 4), 7.2 (m, 2), 7.1 (t, 2), 5 8 (br s, 1), 5.4 (br s, 2), 4.0 (m, 1), 3.4 (m, 2), 3 2 (m, 3), 2 9 (m, 1), 2.5 (m, 2), 2.1 (m, 1), 1.1 (m, 3), 0.8 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-2- (ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.3 (m, 5), 7.1 (t, 2), 6 6 (q, 1), 5 6 (br s, 2), 5.0 (m, 1), 4.4 (m, 0.5), 4.0 (m, 0.5), 3.5 (m, 2), 3 3 (m, 2), 2. 8 (m, 2), 2.7 (m, 1), 2 5 (m, 1), 2.1 (d, 1), 1.2 (m, 3), 0.8 (m, 3) ppm,

(*trans*)-1-((4-chloro-2-((*N'*-(3-methoxyphenyl) ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10 2 (br s, 1), 9.5 (s, 1), 8 5 (br s, 1), 8.2 (s, 1), 7 7 (m, 2), 7 2 (m, 4), 7.0 (s, 3), 6 5 (dd, 1), 5.0 (m, 2), 4 3 (m, 3), 3.7 (m, 5), 3 4 (m, 1), 2 9 (m, 1), 1 4 (s, 3), 1 2 (s, 3) ppm; and

(*trans*)-1-((4-chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.5 (s, 1), 9 0 (m, 1), 8.3 (s, 1), 7.3 (m, 2), 7 0 (m, 4), 4.8 (m, 3), 4 2 (m, 1), 3.6 (m, 2) , 3.4 (m, 1), 3 0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1 3 (m, 3), 0.9 (m, 3) ppm

EXAMPLE 9

Compounds of formula (Ia)

A. To a solution of (*cis*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine (0 20 g, 0.71 mmol) in anhydrous THF (2 mL) was added 4-fluorobenzylbromide (0.11 mL, 0.85 mmol), diisopropylethylamine (0.15 mL, 0 85 mmol) and sodium iodide (0.042 g, 0 28 mmol). The resultant mixture was stirred at ambient temperature for 2 days. At that time the mixture was poured into ether and washed with 5% aqueous $NaHCO_3$ solution, then brine The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil Purification by flash column chromatography on silica gel afforded 0.17 g of (*cis*)-

1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4- fluorobenzyl)piperazine as a pink oil, which was converted to its hydrochoride salt; NMR ($CDCl_3$) 7.6 (m, 2), 7.3 (m, 4), 7.0-6.8 (m, 2), 5 0-2.8 (m, 10), 1 5-1.3 (m, 6) ppm.

B. In a similar manner, the following compounds of formula (Ia) were made

1-((4- chlorophenoxy)methyl)carbonyl-2- ((((cyclopropyl)methyl)amino)methyl)-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 4 5 (s, 2) , 3 4 (m, 4), 3.0 (m, 1), 2.5 (m, 4), 2 2 (t, 1), 2.0 (m, 2), 16 (s, 2), 0 8 (m 1), 0. 5 (m, 2), 0 1 (m, 2) ppm,

(3*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine, hydrochloride salt, NMR ($CDCl_3$) 13.3 (m,1), 7 9 (q, 2), 7.2 (m, 4), 6 9 (d, 2), 6.8 (d, 2), 4.8-3.3 (m, 10), 1 7 (d, 3), 1.2-1 0 (m, 3) ppm;

(3*S*,5*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine, hydrochloride salt; NMR ($CDCl_3$) 13.3 (m,1), 7.9 (q, 2) , 7.2 (m, 4), 6 9 (d, 2), 6 8 (d, 2), 4 8-3.3 (m, 10), 1 7 (d, 3), 1.2-1. 0 (m, 3) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-2-(((4- fluorobenzyl)amino)methyl)-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(((methyl)amino)methyl)-4-(4-fluorobenzyl) piperazine: NMR ($CDCl_3$) 7.3 (m, 4), 7 0 (t, 2), 6 8 (d, 2), 4.5 (q, 2), 3 6 (m, 4), 3.1 (m, 2), 2.8 (m, 3), 2.6 (s, 3), 2.5-2. 3 (m, 3) ppm; and

1-((4-chlorophenoxy)methyl)carbonyl-3- trifluoromethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7 0 (t, 2), 6.8 (dd, 2), 4 6 (m, 2), 4 2 (m, 1), 3.8 (m, 3), 3.6 (dd, 1), 3 3 (m, 2), 3.0 (m, 1), 2 6 (m, 1) ppm.

EXAMPLE 10

Compounds of Formula (Ia)

A To a solution of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2-(methoxycarbonyl)methyl-4-(4-fluorobenzyl)piperazine (0.20 g, 0.42 mmol) in a methanol/water solution (20 mL, 3.1) was added lithium hydroxide, monohydrate (0 40 mL, 9.5 mmol). The resultant mixture was stirred at ambient temperature for 30 min At that time HPLC analysis showed complete conversion had occurred The mixture was poured into ethyl acetate and washed sequentially with an aqueous acetic acid/water solution (pH < 4) , water, and brine The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 0

060 g of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2-(carboxy)methyl-4- (4-fluorobenzyl)piperazine as a white solid; NMR ($CDCl_3$) 7.4 (m, 2), 7.1 (m, 2), 6 2 (m, 2), 5.1 (m, 1), 4.7 (m, 3), 4.0 (m, 2), 3. 8 (d, 9), 3 3-3 1 (m, 4), 2.6 (m, 2), 2.4 (m, 2) ppm, MS (ESI) 476

B. In a similar manner, the following compounds of the invention were made:

1-((4-chlorophenoxy)methyl) carbonyl-3-(carboxy)methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.4 (t, 2), 7 3 (d, 2), 7.1 (t, 2), 6 9 (d, 2), 4.7 (m, 2), 4.0 (d, 2), 3.7 (m, 2), 3.5 (m, 3), 3.2 (m, 1), 2 8-2.4 (m, 3) ppm;

1-((4-chloro-2-carboxyphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8 0 (s, 1), 7 4 (dd, 1), 7 3 (m, 3), 7 0 (t, 1), 6 9 (d, 1), 5.0 (m, 2), 4.6 (m, 1), 4.3 (m, 1) , 3.7 (m, 1), 3.4 (m, 2), 2.8 (d, 1), 2 6 (m, 1), 2.1 (m, 1), 1.4 (d, 1.5), 1.3 (d, 1.5) ppm; and

(*trans*)-1-((4-chloro-2- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 4 (br s, 1), 8.0 (m, 1), 7.5 (m, 3), 7. 2 (m, 2), 7 0 (d, 1), 5 0 (m, 2), 4.6 (m, 1), 4.3 (m, 3), 3.7 (m, 2), 3.4 (m, 1) , 3 3 (m, 1), 1 4-1.3 (m, 6) ppm

EXAMPLE 11

Compounds of formula (Ia)

A. To a solution of lithium aluminum hydride (0.29 g, 7 mmol) in a solution of anhydrous THF (16 mL) was added 1-((4-chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine (0.36 g, 1.0 mmol, in 3 mL of THF). The resultant mixture was stirred at ambient temperature for 9 hours. At that time 0.3 mL of water and 0 3 mL of 15% aqueous NaOH solution were added and the resulting mixture stirred at ambient temperature After 18 hours, the mixture was filtered through a short column of Celite (THF) and the filtrate concentrated *in vacuo* to afford 0.12 g of 1-(2-(4- chlorophenoxy)ethyl)-4-(4-fluorobenzyl)piperazine as a clear oil, NMR ($CDCl_3$) 7.2 (m, 4), 7.0 (m, 2), 6.8 (m, 2), 4 0 (m, 2) , 3 4 (m, 2), 2.8-2 4 (m, 10) ppm

B. In a similar manner the following compounds of formula (Ia) or (Ib) were made·

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid, ^{1}H NMR (400 MHz, DMSO-d_6).δ/ppm = 0.84-0.98 (m, 3H), 1 16-1 28 (m, 3H), 2 16 (m, 1H), 2 70 (m, 1H), 2 88 (m, 1H), 3.08 (m, 0.5H), 3.40 (m, 1 5H), 3.58 (m, 1.5H), 4.0 (m, 1H), 4.40 (s, 0.5H), 4.94 (m, 1.5H), 5 18 (m, 0 5H), 7 12 (m, 3H), 7.36 (m, 2H), 7 54 (m, 1H), 7 62 (s, 1H)5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-

oxoethoxy]benzeneacetic acid, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 1 00 (m, 3H), 1 30 (m, 3H), 2.05 (d, 1H), 2.68 (dd, 1H), 2.80 (m, 1H), 3.05 (m, 1H), 3.25 (m, 1H), 3 60 (m, 4H), 4.10 (m, 1H), 4 65 (m, 2H), 6.78 (m, 1H), 7 00 (t, 2H), 7.33 (m, 4H).

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 1 30 (m, 3H), 2 05 (m, 1H), 2.20 (m, 1H), 2 65 (d, 1H), 2.85 (m, 1H), 3 50 (m, 4H), 3.65 (m, 2H), 4.35 (m, 1H), 4 70 (m, 2H), 6.72 (d, 1H), 7 00 (t, 2H), 7.30 (m, 4H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (400 MHz, DMSO-d_6)·δ/ppm = 0 80-0.98 (m, 3H), 1.16-1.28 (m, 3H), 2.16 (m, 1H), 2.55 (m, 0.5H), 2.70 (m, 0.5H), 2 95 (m, 1H), 3 08 (m, 0 5H), 3.40 (m, 1.5H), 3 58 (m, 1.5H), 4.00 (m, 1H), 4.40 (s, 0.5H), 4 94 (m, 1.5H), 5.18 (m, 0 5H), 7.12 (m, 3H), 7.36 (m, 2H), 7 64 (m, 1H), 7.74 (s, 1H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 0.84-0 98 (m, 3H), 1 16-1 28 (m, 3H), 2.16 (m, 1H), 2.70 (m, 1H), 3 08 (m, 2H), 3 50 (m, 2H), 3 72 (m, 1H), 3 92 (s, 3H), 4.20 (s, 0.5H), 4 94 (m, 2.5H), 6 54 (s, 1H), 7 00 (m, 2H), 7 34 (m, 2H), 8 24 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid; ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm = 0.90 (m, 3H), 1 25 (m, 3H), 2.23 (m, 1H), 2.75 (m, 1H), 3 35 (m, 1H), 3 45 (m, 1H), 3 62 (m, 1H), 3.77 (m, 2H), 3 95 (s, 3H), 4.30 (s, 1H), 5.02 (m, 2H), 6.91 (s, 1H), 7.10 (m, 2H), 7.37 (m, 2H), 7.75 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid; ^{1}H NMR (400MHz, DMSO-d_6 + D_2O):δ/ppm = 0.90-1.10 (m, 3H), 1.20-1 45 (m, 3H), 2.27 (m, 1H), 2 40 (s, 3H), 2.73 (m, 1H), 3.00-4 30 (m, 5H), 4 60-5.10 (m, 3H), 6.84 (s, 1H), 7.02 (m, 2H), 7.30 (m, 2H), 7.98 (s, 1H);

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (400 MHz, DMSO-d_6, 120°C):δ/ppm = 0 94 (d, 3H), 1 24 (d, 3H), 2 25 (d, 1H), 2.75 (dd, 1H), 2.95-3 00 (m, 1H), 3.34 (d, 1H), 3.47 (d, 1H), 3.61 (d, 1H), 3 73 (d, 1H), 4 24-4.30 (m, 1H), 4 94 (d, 1H), 5.03 (d, 1H), 7 09 (dd, 2H), 7 37 (dd, 2H), 7.41 (s, 1H), 7.81 (s, 1H)

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm =

1 00 (m, 3H), 1.30 (m, 3H), 2 30 (m, 1H), 2 70 (m, 1H), 3.10 (m, 1H), 3.25 (m, 1H), 3.60 (m, 2H), 3.70 (m, 1H), 4 65 (m, 1H), 5.00 (m, 2H), 7.00 (t, 2H), 7.30 (m, 3H), 8.05 (s, 1H)

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (500 MHz, DMSO-d_6, 120°C) δ/ppm = 0.62 (t - rotamer, 1.25H), 0.73 (t - rotamer, 3.5H), 0.86 (t - rotamer, 1.25H), 1 24 (m, 1H), 1.37 (m, 1H), 1 54 (m, 1H), 1 69 (m, 1H), 1.84 (m, 1H), 2.26 (t, 1H), 2.57 (d, 1H), 2 66 (dd, 1H), 2 90 (dd, 1H), 3.52 (m, 3H), 4.20 (d, 1H), 4.99 (m – rotamers, 2H), 7.09 (m, 3H), 7.35 (t, 2H), 7.55 (dd, 1H), 7.63 (d, 1H), 13 12 (br, 1H),

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid, ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm = 0.80 (m, 6H), 1.25 (m, 0.5H), 1.40 (m, 1H), 1.70 (m, 4H), 1.94 (m, 1H), 3.08 (m, 4H), 3.90 (m, 3 5H), 4 20 (br, 1H), 4.90 (m, 1H), 5.10 (m, 1H), 6 80 (m, 1H), 7.20 (m, 2H), 7 54 (m, 2H), 7.90 (s, 1H);

5-chloro-4-ethoxy-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

4-amino-5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzoic acid,

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid,

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

4-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid,

2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-5-methylbenzoic acid,

EXAMPLE 12

Compounds of Formula (Ib)

A. To a solution of 1-(1-(*t*-butoxycarbonyl)amino-2-(4-chlorophenyl)ethyl) carbonyl-4-(benzyl)piperazine (0 20 g, 0.44 mmol) in a solution of CH_2Cl_2 (3 mL) was added trifluoroacetic acid (3 mL) The resultant mixture was stirred at ambient temperature After 18 hours, the mixture was concentrated *in vacuo* to afford a

yellow oil. This was dissolved in ethyl acetate and washed with an aqueous $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 0 17 g of a clear, colorless film This was dissolved in ether and treated with an ethereal solution of HCl, resulting in formation of a white precipitate. Concentration afforded 0 18 g of 1-(1-amino-2-(4-chlorophenyl)ethyl)carbonyl-4-(benzyl)piperazine as a white solid; NMR ($CDCl_3$) 7 4 (m, 7), 7 1 (m, 2), 4.0 (t, 1), 3.7-3.1 (m, 4), 2 8 (m, 2), 2 4-2 2 (m, 5), 1 8 (m, 1) ppm.

B. In a similar manner, the following compounds of formula (Ib) were made

1-(3-amino-2-(4-chlorophenyl)propyl) carbonyl-4-(4-chlorobenzyl)piperazine; NMR ($CDCl_3$) 7 2 (m, 8), 3.8 (s, 3), 3 6-3 3 (m, 8), 3 0 (m, 2), 2.6 (dq, 2), 2.4-2.1 (m, 4) ppm; and

1-(1-amino-2-(4-chlorophenyl)ethyl)carbonyl-4-(4- chlorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 6), 7.1 (d, 2), 4.0 (t, 1), 3 6-3 1 (m, 6), 2 8 (dq, 2), 2.6 (br s, 2), 2.4 (m, 3) , 1.8 (m, 1) ppm.

C. In a similar manner, the following compounds of formula (Ia) were made.

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7. 3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (br d, 1), 4.7 (m, 2), 3 9 (s, 2), 3. 5 (m, 3), 3 0 (br s, 1), 2.7 (m, 1), 2 2 (m, 4), 1 3 (m, 3), 0.9 (m, 3) ppm;

(trans)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.1 (s, 1), 8.5 (s, 1), 7 3 (t, 3), 7.0 (t, 3), 6 8 (d, 1), 4.7 (m, 3), 4.2-3. 4 (m, 5), 3 2 (m, 1), 3 0 (br s, 1), 2.7 (dd, 1), 2 2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(2*R*,5*S*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.0 (s, 1), 8 2 (m, 3), 7 6 (s, 1), 7 3 (m, 2), 7.1 (dd, 1), 6 9 (m, 1), 5 2-4.2 (m, 5), 3 8-2 9 (m, 7), 1.2 (m, 6) ppm,

(2*R*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11. 4 (br s, 1), 10.0 (s, 1), 8.3 (br s, 2), 8 1 (s, 1), 7 8 (m, 2), 7.4 (t, 2), 7 1 (d, 1), 7.0 (d, 1) 5 0 (q, 2), 4 7 (m, 1), 4 3 (m, 3), 3.9 (m, 3), 3.6 (m, 1), 3.1 (m, 3), 1.5 (d, 1.5), 1.3 (d, 1 5) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.9 (s, 1), 8 5 (s, 1),

7.3 (m, 3), 7 0 (m, 3), 6.8 (d, 1), 4 7 (m, 3), 4.2-3.9 (m, 1), 3 6-3.3 (m, 5), 3.0 (br s, 1), 2 7 (dd, 1), 2 5 (s, 3), 2.3 (d, 1), 1.3 (m, 3), 1 0 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10. 2 (s, 1), 8 5 (s, 1), 7 3 (m, 3), 7.0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 4.2- 3.9 (m, 1), 3.6-3.2 (m, 5), 3 0 (m, 1), 2 7 (dd, 1), 2 2 (d, 1), 1.4 (d, 3), 1.3 (m, 3), 1.0 (br s, 3) ppm;

(*trans*)-1-((4-chloro-2- (1-(methylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 3), 7.1 (dd, 1), 7 0 (t, 2), 6 8 (br d, 1), 4.7 (m, 3), 4.0 (q, 2), 3.6 (q, 2), 3. 2 (m, 1), 3.0 (m, 1), 2 7 (dd, 1), 2.3 (m, 4), 1.3 (m, 6), 0 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.6 (br d, 1), 74-7.1 (m, 8), 7.0 (t, 2), 6.8 (m, 1), 5.0 (d, 1), 4.6 (m, 3), 4 2 (m, 1), 3 5 (t, 1), 3.4-3 0 (m, 4), 2. 8 (m, 1), 24 (s, 3), 2.2 (m, 1), 1 2 (m, 3), 0.8 (m, 3) ppm,

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazineNMR (DMSO-d_6) 9 2 (br s, 1), 7.6 (m, 4), 7 3 (t, 2), 7.2 (d, 1), 5.2 (dd, 1), 5. 0 (d, 1), 4 8 (m, 1), 4.4 (d, 4), 3.9 (d, 1), 3 4 (m, 11), 1.4 (d, 1 5), 1. 2 (d, 1.5) ppm;

(2*R*,5*S*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.8 (br s, 1), 9 2 (br s, 1), 7.6 (s, 3), 7 5 (dd, 1), 7.3 (t, 2), 7.2 (d, 1), 5.4 (m, 1) , 5 0 (m, 3), 4.7 (m, 1), 4.5 (s, 2), 4 3 (m, 3), 3.7-3.1 (m, 11), 1.4-1. 1 (m, 6) ppm,

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO- d_6) 11.3 (br d, 1), 9 7 (m, 2), 7.9 (m, 2), 7 7 (m, 2), 7. 4-7.2 (m, 3), 5 4 (m, 1), 5.0 (m, 2), 4.6 (m, 1), 4.2 (m, 3), 3.8-3 2 (m, 10), 2 8 (dd, 1), 1 7 (m, 3), 1 4 (dd, 3), 1 2 (m, 3) ppm,

(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 4), 7. 2 (d, 2), 7.0 (t, 2), 4 8 (m, 1), 4.2 (m, 1), 3.9 (m, 1), 3 5-3 2 (m, 3), 2 9 (m, 3), 2.6 (m, 2), 2.2 (m, 1), 1 2 (m, 3), 0.8 (m, 3) ppm; and

(*trans*)-1-(2-(4-chlorophenyl)-2-(amino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 6), 7.0 (t, 2), 4.7 (m, 0 5), 4 5 (m, 1), 4 2 (d, 0 5), 3 5 (q, 2), 3. 2 (m, 1), 3.0 (m, 1), 2 6 (m, 2), 2 5 (m, 2), 2.2 (m, 1), 1 2 (m, 3), 0 9 (m, 3) ppm

EXAMPLE 13

Compounds of Formula (Ia)

A. To a solution of (*trans*)- 1-((4-chloro-2-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine (0.217 g, 0 50 mmol) in a solution of tetrahydroduran (5 mL) at 0°C was added isobutyl chloroformate (0.075 g, 0.55 mmol) and *N*-methylmorpholine (0.0556 g, 0 55 mmol) The resulting mixture was stirred at 0°C for 20 min, resulting in formation of a white precipitate A solution of methylamine in tetrahydrofuran (0. 25 mL, 2.0 M, 0.50 mmol) was then added and the mixture stirred for 30 min more, at which time it was concentrated of volatiles *in vacuo*. The resulting residue was dissolved in ethyl acetate and washed with water, then brine, dried over $MgSO_4$, filtered and concentrated to 0 208 g of a foam. This was dissolved in ethyl acetate and treated with 1 M ethereal HCl solution (excess). The resulting solid was collected by filtration and washed with ethyl acetate. Drying *in vacuo* afforded 0 19 g of (*trans*)-1-((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine as a white solid; NMR (DMSO-d_6) 10.8 (br d, 1), 9.2 (br s, 1), 7 8 (s, 2), 7.7 (m, 1), 7.6 (m, 1), 7 3 (m, 3), 5 4 (d, 1), 5 0 (m, 2), 4.7 (m, 1), 4 3 (m, 3), 4 0 (m, 1), 3.6 (m, 2), 2. 8 (s, 3), 1 4 (m, 3), 1.3 (m, 3) ppm.

B In a similar manner, the following compounds of formula (Ia) were made

(*trans*)-1-((4-chloro-2-((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 9 4 (br s, 1), 7 8 (s, 1), 7 6 (dd, 1), 7.4 (m, 2), 7.2 (d, 1), 7.1 (t, 2), 7 0 (s, 1), 5 3 (m, 1), 5.0 (m, 2), 4 4 (m, 1), 4.0 (m, 1), 3.8 (d, 2), 3.5 (m, 2) , 3 0 (m, 1), 2.7 (m, 1), 2.2 (br d, 1), 1.2 (br d, 3), 0.9 (br d, 3) ppm;

(*trans*)-1-((4-chloro-2-((2-aminoethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 9 4 (br s, 1), 8 2 (s, 1), 7 3 (m, 3), 7 0 (t, 2), 6.8 (d, 1), 4 7 (m, 3), 4 2 (m, 1) 3 6 (m, 5), 3.1 (m, 3), 2.7 (br d, 1), 2.3 (d, 1), 1 3 (br d, 3), 1 0 (m, 2) ppm,

(*trans*)-1- ((4-chloro-2-((4-aminocarbonylphenyl)aminocarbonyl)phenoxy)methyl) carbonyl-2 5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR (DMSO-d_6) 11.4 (s, 1), 7 9 (m, 5), 7 7 (d, 1), 7.4 (m, 3), 7 1 (t, 2), 5 4 (d, 1), 5.1 (m, 2), 4 6 (br s, 1), 4.0 (m, 1), 3 5 (m, 3), 3 0 (m, 1) , 2 2 (m, 1), 1.3 (m, 3), 0 9 (m, 3) ppm; and

(*trans*)-1-(2-(4-chlorophenyl)-3-(*t*-butoxycarbonylamino)propyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7 3 (m, 4), 7.2 (d, 2),

7.0 (t, 2), 4.8 (br s, 1), 4.6 (m, 1), 4 0 (m, 1), 3.4 (m, 6), 3.0 (m, 1), 2.6 (m, 2), 2.1 (m, 1), 1.4 (s, 9) , 1.2 (m, 3), 0.9 (m, 3) ppm

EXAMPLE 14

Compounds of formula (Ia)

A To a solution of hydroxylamine, hydrochloride (0.17 g, 2 5 mmol) in DMSO (3 mL) was added triethylamine (0.252 g, 2.5 mmol). The mixture was stirred at ambient temperature for 10 minutes, then filtered and washed with THF. The filtrate was concentrated *in vacuo* to remove the THF then treated with (*trans*)-1-((4-chloro-2-cyanophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine (0.200 g, 0 48 mmol). The resulting mixture was heated to 75°C for 20 hours At that time the mixture was diluted with water and extracted with ethyl acetate The organic extract was washed with water, then brine, dried over $MgSO_4$, filtered concentrated *in vacuo* to afford 0 21 g of an oil. 0.030 g of this oil was dissolved in ethyl acetate and treated with 1 M ethereal HCl solution (excess) The resulting solid was collected by filtration and washed with ethyl acetate. Drying *in vacuo* afforded 0.027 g of (*trans*)-1-((4-chloro-2-(hydroxyamidino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine as a white solid; NMR ($CDCl_3$) 7.6 (s, 1), 7.3 (t, 2), 7.2 (dd, 1) , 7.0 (t, 2), 6 7 (br d, 1), 6 1 (br s, 2), 4.7 (m, 3), 3.7 (br d, 1), 3 5 (q, 2), 3 2 (m, 1), 3.0 (m, 1), 2 7 (m, 1), 2.2 (t, 1), 1.3 (m, 3), 0.9 (m, 3) ppm.

EXAMPLE 15

Compounds of Formula (Ia)

A To a solution of 4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)piperazine (0 134 g, 0.33 mmol) and triphenylphosphine (0.100 g) in THF (6 mL) at 0°C was added diethyl azodicarboxylate (0 060 mL) and diphenylphosphoryl azide (0.081 mL) The mixture was stirred at ambient temperature for 2 days, then concentrated of volatiles *in vacuo*. Purification by flash column chromatography on silica gel afforded 0.047 g of 1-((4-chlorophenoxy) methyl)carbonyl-2-(2-azidoethyl)-4-(4-fluorobenzyl)piperazine as a clear, colorless oil, NMR ($CDCl_3$) 7 3 (m, 4), 7 0 (t, 2), 6 9 (d, 2), 4 7 (m, 3), 4.4 (br d, 1), 4 3 (m, 1), 4.1 (m, 1), 3 5-3 1 (m, 4), 2.8 (d, 1), 2 7 (d, 1), 2.1 (m, 2), 1.8 (m, 1) ppm

EXAMPLE 16

Compounds of Formula (Ia)

A. To a solution of (*trans*)-1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine (0.169 g, 0.416 mol) in 10 mL of methylene chloride was added phthallic anhydride (0.074 g, 0 499 mol) and several 4Å molecular sieves The mixture was stirred at ambient temperature for 3 hours, then at 70°C for 3 hours. At that time the mixure was cooled to 0°C and treated with oxalyl chloride (0 064 g, 0.499 mol) This was stirred at ambient temperature for 3 hours then partitioned between methylene chloride and water. The organic layer was concentrated to give an oil. Purification by flash column chromatography on silica gel afforded 0 058 g of a clear oil. This was dissolved in ethyl acetate and treated with 1 M ethereal HCl solution (excess). The resulting solid was collected by filtration and washed with ethyl acetate. Drying *in vacuo* afforded 0.045 g of (*trans*)-1-((4-chloro-2-(phthalimido)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine as a white solid, NMR ($CDCl_3$) 7 9 (m, 2), 7.8 (m, 2), 7.4 (d, 1), 7 3 (m, 3) , 7 05 (d, 1), 7.0 (t, 2), 4 6 (m, 3), 4.0 (m, 1), 3 5 (m, 1), 3.4 (m, 2), 2.9 (m, 1), 2.6 (m, 1), 2 2 (m, 1), 1 2 (m, 3), 0.9 (m, 3) pppm.

B In a similar manner, the following compound of formula (Ia) was made.

(*trans*)-1-((4-chloro-2-(maleimido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, NMR ($CDCl_3$) 7 3 (m, 6), 7 0 (t, 2), 6 8 (s, 1), 4.6 (m, 3) , 4.0 (m, 1), 3.5 (q, 2), 3 2 (m, 1), 3 0 (br s, 1), 2.6 (dd, 1), 2 2 (br d, 1), 1 2 (m, 3), 0.9 (m, 3) ppm.

EXAMPLE 17

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e g* , 1-((2- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine hydrochloride salt.

A. Ingredients	% wt./wt.
Compound of the invention	20 0%
Lactose	79 5%
Magnesium stearate	0 5%

The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each, one capsule would approximate a total daily dosage

B. Ingredients	% wt /wt.
Compound of the invention	20.0%
Magnesium stearate	0.9%

Starch	8 6%
Lactose	69.6%
PVP (polyvinylpyrrolidine)	0 9%

The above ingredients with the exception of the magnesium stearate are combined and granulated using water as a granulating liquid The formulation is then dried, mixed with the magnesium stearate and formed into tablets with an appropriate tableting machine

C. Ingredients

Compound of the invention	0.1 g
Propylene glycol	20.0 g
Polyethylene glycol 400	20.0 g
Polysorbate 80	1.0 g
Water	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 mL of the solution which is filtered and bottled.

D Ingredients	% wt /wt.
Compound of the invention	20 0%
Peanut Oil	78. 0%
Span 60	2 0%

The above ingredients are melted, mixed and filled into soft elastic capsules.

E. Ingredients	%wt./wt
Compound of the invention	1.0%
Methyl or carboxymethyl cellulose	2.0%
0.9% saline	q s 100 mL

The compound of the invention is dissolved in the cellulose/saline solution, filtered and bottled for use.

EXAMPLE 18

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e. g.*, 4- (4-fluorobenzyl)-1-((2-((acetylamino)methyl)-4-chlorophenoxy)methyl) carbonyl-2,5-methylpiperazine:

Ingredients

Compound of the invention	0 02 g
Propylene glycol	20 0 g
Polyethylene glycol 400	20 0 g

Polysorbate 80	1 0 g
0 9% Saline solution	q s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I V. solution which is filtered through a 0 2 m membrane filter and packaged under sterile conditions.

EXAMPLE 19

This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 4- (4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl) piperazine

Ingredients	% wt./wt.
Compound of the invention	1 0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

EXAMPLE 20

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g , (2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,5-dimethylpiperazine.

Ingredients	% wt./wt.
Micronized compound of the invention	1.0%
Micronized lactose	99.0%

The ingredients are milled, mixed, and packaged in an insufflator equipped with a dosing pump

EXAMPLE 21

This example illustrates the preparation of a representative pharmaceutical formulation in nebulized form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 1-(((4- chlorophenyl)amino)methyl)carbonyl-4-(4-chlorobenzyl)piperazine:

Ingredients	% wt./wt.

Compound of the invention	0.005%
Water	89.995%
Ethanol	10 000%

The compound of the invention is dissolved in ethanol and blended with water. The formulation is then packaged in a nebulizer equipped with a dosing pump.

EXAMPLE 22

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 1-((4-chloro-2-(((ethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine:

Ingredients	% wt./wt.
Compound of the invention	0.10%
Propellant 11/12	98 90%
Oleic acid	1. 00%

The compound of the invention is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

In the following examples, 293MR cells are utilized. These are human embryonic kidney cells (HEK293) which were stably transfected to express human CCR1 receptor by the following procedure: HEK293 cells were obtained from the American Type Culture Collection (ATCC CRL 1573). Human CCR1 cDNA was provided through collaboration with Dr. Stephen Peiper of the University of Louisville, Kentucky The CCR1 gene was subcloned using standard techniques (see, e .g , *Molecular Cloning. A Laboratory Manual, 2nd Edition, Cold Spring* Harbor Laboratory Press, 1989) into a standard plasmid containing the SV40 promoter and enhancer. The plasmid also contained hygromycin and puromycin resistance genes Calcium phosphate transfection standard protocols were used to insert the plasmid into the HEK293 cells Cells were selected for stable expression of CCR1 using hygromycin and puromycin selection. Cells were tested for the ability to bind ^{125}I- labelled RANTES or MIP-1α with high affinity

EXAMPLE 23

In Vitro Assay: Calcium Flux

Since the CCR1 receptor, in common with other seven transmembrane G-protein coupled receptors, responds to the binding of its ligand, *e.g.*, MIP-1α and RANTES, by mobilizing free intracellular calcium, one can measure biological activity by calcium flux assays using the fluorescent dye Fura 2. In the following assay, the ability of the compounds of the invention to block this biologic response is measured

Protocol.

1) Two flasks of 293MR cells were detached, washed and resuspended in Hanks Ca^{2+} (50 mL Hanks, 1.0 mL 1 M Hepes, 1 6 mL 500 mM $CaCl_2$, pH 7 4) The cells were washed twice in this media.
2) The cells were counted CCR1 = 28 x 10^6 cells made to 2 x 10^6 cells/mL by suspending into 14 mL Hanks Ca^{2+}.
3) To 10 mL of the cells (20 x 10^6) was added 30 mL of media (containing 50 μg of Fura in 50 μL of DMSO). Final cell concentration was 1.0 x 10^6 cells/mL Final Fura concentration was 1 25 μM.
4) The cells were incubated at 37°C for 30 minutes in the presence (or absence) of increasing concentrations of compounds of the invention Cells were washed as above to remove free Fura Cells were resuspended at 1 x 10^6 cells/mL. Cells were then aliquoted (2 0 mL) in a cuvette and placed in a spectrofluorimeter. The cells were then stimulated with either MIP-1α or RANTES (Peprotech Inc) and Ca^{2+} release was measured in the spectrofluorimeter
5) The data were corrected for nM Ca^{2+} released by adding 100 μL of 0.1 % Triton X-100 (for maximum values) followed by 100 μL of 500 mM EGTA, pH 8.5 (for minimum values)

The compounds of the invention, when tested in this assay, demonstrated the ability to inhibit the Ca^{2+} mobilization in response to binding of MIP-1α and RANTES to the CCR1 receptor

EXAMPLE 26

In Vitro Assay

The assays were performed in a microphysiometer to investigate the functional activity of the antagonist of interest The microphysiometer assesses cellular response through the use of a silicon-based potentiometric sensor that can measure small changes on solution pH (Hafeman *et al*, *Science* (1988), Vol. 240, pp. 1182-1185; Parce *et al*, *Science* (1989), Vol 246, pp 243-247) It has been shown that the microphysiometer can be used for measuring metabolic rates of living cells (Parce *et al*, 1989). The activation of cell membrane receptors can alter the rate of extracellular acidification

(Owicki *et al*, *Proc. Natl Acad. Sci* (1989), Vol. 87, pp. 4007-4011) The following assay demonstrates that activation of CCR1 receptors endogenously expressed on human THP-1 cells with MIP-1α and RANTES induced physiological changes resulting in an increase in metabolic rates and that the compounds of the invention inhibit this effect in a dose-dependent manner

Materials

1 Cytosensor Capsule Kit (Molecular Devices Cat #R8013).
2. Agarose Entrapment Medium (Molecular Devices Cat # R8023)
3. Cytosensor Modified RPMI 1640 Medium, low buffered (Molecular Devices Cat #R8023)
4 Cytosensor Sterilant Kit (Molecular Devices Cat# R8017)
5. Reference Electrode Maintenance Kit (Molecular Devices Cat# 0310-2805)
6. MIP-1α or RANTES (Peprotech Inc.) working solution: 10 μM in Modified RPMI 1640 medium (Molecular Devices Cat# R8016) supplemented with 1 mg/mL BSA (bovine serum albumin),100 units/mL penicillin, and 100 μg/mL streptomycin). This working solution is hereinafter referred to as "modified culture medium".
7. MCP-1 working solution 10 μM in modified culture medium
8 Compounds of the invention stock solution. 1 mM in DMSO (stored at ambient temperature)
9. Cell Culture
   a. THP- 1 (ATCC Cat #TIB202)
   b. Tissue culture medium: RPMI 1640 supplemented with 10% FBS (fetal bovine serum). This medium is hereinafter referred to as "growth medium".

Assay Procedure·

THP-1 cells were grown in T-25 cm^2 flasks in growth medium at 37° C, 5 0% CO_2, 95% air to a cell density of $1x10^6$ cells/mL The cells were harvested by centrifugation (5 minutes at 20 G) and resuspended in modified growth medium. Trypan blue dye exclusion cell count was performed and cells were ≥ 90% viable. Cells were centrifuged again, the supernatant was removed, and the resulting pellet was resuspended to final cell concentration of 1×10^6 /0.1 mL Agarose cell entrapment reagent was melted and placed into a 37°C water bath. Cell suspension was prepared. 0 15 mL of the THP-1 cells were added to a 1 5 mL centrifuge tube with 50 μL of the melted agarose solution Addition to the capsule cups. the capsule cups were placed in a 12 well microtiter plate, a spacer was added to the capsule cup, and 7 μL of cell/agarose suspension was pipetted into the center of the cup After three minutes, 1 mL of modified growth medium was pipetted to the outside of the capsule cup, and 200 μL of modified growth

medium was pipetted to the inside. The capsule insert was then placed into the cup with sterile forceps and 500 µL of modified culture medium was pipetted into the insert. Completed capsule were loaded into the chambers of the microphysiometer. The chambers were perfused at a rate of 100 µL/minute with modified culture medium. The pump cycle was 50 seconds on and 40 seconds off Multiple data points representing metabolic rate were taken and used as baseline. Cells were exposed to the compounds of the invention for 30 minutes prior to addition of chemokine agonists at a final concentration of 10 nM. Treated and non-treated cells were challenged with agonist for 100 seconds and data was collected

When tested in this assay, the compounds of the invention demonstrated the ability to inhibit the activation of the CCR1 receptor by MIP-1α or RANTES

EXAMPLE 25

In vitro assay for CCR1 receptor antagonists.

This assay demonstrates the affinities of the compounds of the invention for binding to the CCR1 receptor The binding affinities of the compounds for the CCR1 receptor were determined by their abilities to compete with ^{125}I-MIP-1α or ^{125}I-RANTES for binding to the CCR1 receptor.

Reagents and Solutions, MIP-1α and RANTES (Peprotech Inc)

Cells:

293MR cells (K_D=1-3 nM and B_{max}=2-3 x 10^6 sites/cell) were detached by trypsinization and plated into flasks at least 48 hours prior to the experiment.

Ligand

^{125}I-MIP- 1α and ^{125}I-RANTES from New England Nuclear (specific activity is 2200 Ci/mmol, 25 µCi/vial) was reconstituted in 1 mL H_2O.

Assay buffer·

- 130 mM NaCl, 5 mM KCl, 1 mM $MnCl_2$, 50mM Tris, 30 µg/ml bacitracin, 0 1% BSA, pH 7 4

Wash buffer

Phosphate buffer solution (PBS)

Compounds of the Invention:

The stock solution of the compounds was 1 mM in 100% DMSO. The highest concentration in the assay was 10 µM and may vary depending on the potency of the compounds. A serial 1.3 dilution from the highest concentration was made with assay buffer. Six concentrations of each compound were usually being screened to generate a dose curve from which the K_i value was determined.

Assay procedure

Assays were performed in 96-well v-bottom microtiter plates in a total volume of 100 µl 293MR cells was detached from T225 cm^2 flask in PBS by shaking. The cells were washed once in PBS and resuspended in the assay buffer to about 1.1 x 10^5 cells/mL. Cells (about 8000 cells/assay) were incubated with either ^{125}I-MIP-1α or ^{125}I- RANTES (about 15,000-20,000 cpm/assay) in the presence and absence of different concentrations of compounds at ambient temperature for 30-40 minutes

The reactions were terminated by harvesting through a GF/B filter plate presoaked with 0 3% PEI (Sigma # P- 3143) plus 0.5% BSA and washing 5 times with cold PBS. The radioactivities in each well were determined by scintilation counting following addition of 50 µl of scintillation fluid.

The nonspecific binding was defined by the binding in the presence of 100 nM of unlabeled MIP-1α or RANTES. The CCR1 receptor concentration used in the assay was 0.4 nM and ^{125}I- MIP-1α or ^{125}I-RANTES was 0 06 nM The concentrations of compounds in the assay is typically from 10 µM to 30 nM in 1:3 dilution and the concentrations for more potent compounds were lower depending on the potency.

Calculations:

The dose curves of each compound with 6 concentration points were generated and IC_{50} values were determined by fitting the data to the log-logit equation (linear) with an EXCEL spread-sheet The K_i values were then calculated by dividing the IC_{50} by 1.025, to correct for concentration of labelled ligand.

The compounds of the invention, when tested in this assay, demonstrated their affinity to bind to the CCR1 receptor.

The data given in Table 2 show that the compounds listed bind to CCR1 receptor and compete with MIP-1α and RANTES. The K_i values are in the range of 1-172 nM

Table 2 is only a selection of compounds tested.

A comparison with other known piperazine compounds is given in Table 1 The compounds according to the present application (No 10-12) have superior binding affinities to the CCR1 receptor compared to compounds which are alkylated at α-carbon (No. 1-6, 13) and compounds which have no substitution on the piperazine ring (No. 1-9). For example compounds 1-6 have K_i values of grater than 10 µM

Examle 26

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Effects of a CCR-1 antagonist on cell migration/chemotaxis will be analyzed on human U937 cells and peritoneal macrophages, isolated from peritoneal fluid from patients with endometriosis and controls.

Chemotaxis will be assayed in Boyden chambers containing permeable 0.4 µm pore size polyethylene terephthalate (P E.T) track-etched membranes (Becton Dickinson, Franklin Lakes, NJ). In this assay, a human histiocytic cell line (U937) that can be induced to display monocytic differentiation and chemotactic responsiveness after treatment with 1 mM 8-bromo-cyclic adenosine monophosphate (cAMP) (Kay et al. 1983)

U937 cells are cultured at 37°C with 5% CO_2 in RMPI medium supplemented with 10% fetal calf serum and penicillin G (100 U/mL), streptomycin (100 µg/mL) and gentamicin (50 µg/mL) and incubated with 1 mM 8-bromo-cAMP (Sigma, St Louis, MO) every 24 hours for a total of 48 hours The presence of CCR-1 protein in U937 cells and peritoneal macrophages will be confirmed by Western Blot analysis· 50 µg of protein lysates from U937 cells will be subjected to SDS-PAGE and the proteins will be blotted to nitrocellulose paper as described (Homung et al 1997). Mouse IgG monoclonal antibodies will be raised against the human RANTES receptor CCR-1.

A peritoneal fluid pool of 16 patients with moderate or severe endometriosis will be prepared. The protein amount of RANTES will be measured with specific ELISAs (R&D Systems). Samples are diluted 1.4 in PBS with 0 1% BSA and placed in the bottom wells of the Boyden chambers (600 µL per well). P.E.T track-etched membranes are then fixed in place in 24 well plates to separate bottom from top compartments and 500 000 cells in 200 µL of PBS containing 0 1% BSA will be added to the upper wells. Before the experiments starts, cells will be preincubated for 30 min with CCR1 antagonist As control, cells will be treated with PBS. The loaded chambers will be incubated at 37°C in humidified air with 5% CO_2 for 120 minutes. Nonmigrating cells will be removed by several washes with PBS and migrating cells will be fixed to the membrane with absolute methanol overnight at 4°C and stained with Crystal Violet (Sigma, St Louis, MO) Optical absorption at a wavelenght of 570nm is used to quantify monocyte chemotaxis The same peritoneal fluid pool will always be used as a positive control and values normalized to 100% in each set of experiments PBS alone will always be used as a negative control.

To evaluate the inhibitory effects of CCR-1 antagonist, the same peritoneal fluid pool of 16 patients with moderate or severe endometriosis will be used CCR1 antagonist will be added at concentrations of 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7} or 10^{-6} molar.

Apoptosis ELISA

Programmed cell death by apoptosis is characterized by formation of multinucleosomal-sized genomic DNA fragments. DNA fragments are multiples of 180 bp subunits associated with core histones The levels of DNA released in the cytosol of apoptotic cells will be measured using the Cell Death Detection ELISA kit (Roche, Mannheim, Germany) This is a quantitative sandwich-enzyme-linked-immunoassay using antibodies against DNA and histones. Extent of DNA fragmentation is expressed as an enrichment factor, calculated by dividing the absorbance of a given sample by the absorbance of the corresponding 10% FCS control

Assessment of apoptosis in CCR-1 treated U937 cells

One potential mechanism of chemotaxis inhibition is via monocyte apoptosis. To exclude this potential mechanism, we will use a DNA fragmentation ELISA U937 cells will be cultured for 24h in 10% (control) and 2.5% FCS. Samples in 2.5% FCS will be incubated with CCR-1 antagonist (ZK811752) Cells treated with TNF-alpha in 2.5% FCS will be used as a positive control

Statistical analyses

All experiments will be repeated three times and results will be expressed as the mean ± SD. Normally distributed data will be analyzed by paired t-test or ANOVA. Nonparametric data will be analyzed by the Kruskal-Wallis and Mann-Whitney statistics. Significant differences will be accepted when two-tailed analyses yield $P<0.05$

Example 27

Determination of CCR1 mRNA in endometrial and endometriotic tissue samples by real-time quantitative RT-PCR analysis.

Total RNA from endometrium and endometriotic lesions was extracted using Trizol Reagent (Life Technologies,cat no·15596-026). Afterwards 20 µg of total RNA was used to enrich poly (A) +RNA (Medcalf et al ; EMBO J 1986; 5, 2217)

The cDNA synthesis was performed by using SuperScript First-Strand Synthesis System (Invitrogen) Quantification of mRNA abundance was performed by real-time PCR detection using an ABI PRISM 7700 Sequence Detection System (PE Biosystems, Inc , Weiterstadt, Germany) and SYBRGreen as double stranded DNA-specific fluorescent dye (SYBRGreen PCR Master MIX, PE Biosystems) For

quantification of amplified transcripts, 0.2 µl first strand cDNA was used Relative Quantification with data from the ABI PRISM 7700 sequence Detection System was performed using the comparative CT method.
Specific primer pair for CCR1 detection : 5'-CTC-CGT-GCC-AGA-AGG-TGA-AC-3' and 5'-CCA-GGA-CCA-CCA-GGA-TGT-TT-3'. Internal control and reference gene was the housekeeping gene cyclophilin (Primer pair: 5'-GAA-GTT-GGC-CGC-ATG-AAG-A-3' and 5'-GCC-TAA-AGT-TCT-CGG-CCG-T-3'). PCR reaction: 10 min 95°C, 15 sec 95°C, 1 min 62°C (40 cycles). The purity of amplification products were controlled by melting curves

Example 28

Immunohistochemical analysis of CCR1 in endometriotic lesions and in endometrium. Biopsies were frozen at the point of collection and stored at –80°C. For cutting, tissues were first embedded in TissueTek (Sakura) and equilibrated at –20°C Before immunostaining, frozen slides were thawed and air-dried for 2 hours at room temperature.
For immunohistochemical analysis tissue sections were then cut using a Leica Kryotome and mounted on SuperFrost Plus glass slides Cryosections of 5 µm were performed and fixed for 10 min in Aceton at 4°C. The fixed cryosections were washed in TBS and blocked with peroxidase block solution (DAKO). After a next washing procedure the tissue slides were blocked for 15 min with protein block solution from DAKO.
Tissue from peritoneal lesions and endometrium were incubated for 30 min with a monoclonal CCR1 antibody (clone 53504 111, R&D Systems) in a concentration of 0.8 µg/ml. Immunohistochemical stainings were performed with goat anti-mouse DAKO EnVision System, Peroxidase (AEC) Kit (DAKO K4004). The samples were washed and incubated with EnVision-System peroxidase labelled polymer (DAKO). After 15 min AEC-Chromogen incubation the samples were washed and incubated for 5 min in Haematoxilin. Stained tissues were embedded in Fluoromount G (Dunn Labortechnik GmbH) For characterization of CCR1 expressing immune cells, the samples were stained with antibodies for CD4/CD14 and CD68 (Dako) and Alexa 568 (Molecular Probes) Stained tissues were examined with an Axioplan imaging microscope Pictures were taken with the AxioCam Camera System, Axiovision 3 1, KS400 (Carl Zeiss) All images were taken with the same exposure time

Example 29

Effects of compounds according to the present invention on surgically induced endometriosis in intact cycling rats.

Surgical procedure Endometriosis was induced surgically in female Wistar rats (200g-250 g body weight) showing a normal 4 day oestrous cycle All procedures were carried out under sterile conditions. During the first laparotomy, a 2 cm portion of the right uterine horn was resected and placed in PBS at 37°C The uterine segment was opened longitudinally, and the endometrium was peeled from the myometrium. One segment was transplanted to the parietal peritoneum of the right abdominal wall and the other segment to the arterial cascades of the intestinal mesentery. The segments were sutured using non-absorbable silk suture at four corners, with the endometrial surface facing the lumen of the peritoneal cavity. At 4 weeks after the induction of endometriosis, the animals underwent a second laparotomy to evaluate the size and viability of the ectopic endometrial tissue. Macroscopically, this laparotomy revealed the formation of cystic structures (endometriosis-like foci) in ~90% of the animals. The surface area in length X width (mm^2) was measured using a calliper. Only animals in which the ectopic endometrium had formed endometriosis-like foci at both locations were used for the experiment The animals were divided into 4 groups (n=10 animals per group). Group 1 animals (controls) received vehicle only. Group 2 animals were treated with an anti estrogen (positive control reference) (dose 1 mg/kg) daily Group 3 received 50 mg/kg with (2R)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as chloride salt two times daily. Group 4 sham operated animals Groups 1-3 were treated with daily s c. injections for 4 weeks

Evaluation· The animals were killed with a CO2 atmosphere after 4 weeks of treatment. During autopsy, the number of animals with or without persistent endometriotic lesions was calculated and the and the surface area and the volume was measured in situ. The mRNA expression of CCR1 and RANTES in rat uterus, ovary, peritoneal and mesenteral endometriotic cysts was analysed and quantified as described in Example 27.

Example 30

Endometriosis is experimentally induced by the inoculation of menstrual endometrium or by autologous transplantation as described in the literature (11, 12, 13, 14) Immunoistochemical analysis of CCR1 in endometriotic grafts/lesions were performed as described in Example 28.

First part of the study: Endometriosis treatment. After induction of endometriosis, primates were treated with different concentrations of CCR1 antagonist for 2-3 weeks. As control, animals will be treated with vehicle, GnRH antagonist and Placebo. A videolaparoscopy will be performed to document the number, surface, volume and revised American Fertility Society (rAFS) score and stage of endometriotic lesions All laparoscopies were performed by a single investigator Serum and blood samples were taken and analyzed before induction of the disease and during treatment. In the second part of the study, animals were treated with CCR1 antagonist before endometriosis was induced, particularly with (2R)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as sulphate salt At study end, endometriotic lesions were subjected to immunohistochemical and molecularbiological analysis.

Example 31

Efficacy of CCR1 antagonist according to the invention in the treatment of symptomatic endometriosis.

The following clinical study is performed to examine the efficacy of CCR-1 antagonists according to the invention, particularly (2R)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as sulphate salt for the treatment of endometriosis and associated pelvic pain.

A multi-center, placebo-controlled, randomized, double-blind in parallel-groups study is designed with a population of young fertile women with historically confirmed endometriosis in the age of 18 – 45 years, with or without infertility

The study will be Placebo-controlled, randomized, double-blind in parallel-groups. The duration of the treatment is of three months.

The primary efficacy variable is change of pelvic pain by visual analogue scale

Secondary efficacy variables: Reduction of intake of co-medication for pelvic pain.

Safety parameters Physical and gynaecological examination incl. breast, safety laboratory, bleeding patterns (patient diary).

The invention is described above with reference to preferred forms of embodiment It is nevertheless clear that the invention is susceptible to numerous variations within the framework of technical equivalents.

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Cited Literature

1 Neote, K., DiGregono, D., Mak, J Y., Horuk, R , and Schall, T.J 1993 Molecular cloning, functional expression, and signaling characteristics of a C-C chemokine receptor Cell 72 415-425.

2. Su, S.B., Mukaida, N , Wang, J., Nomura, H., and Matsushima, K. 1996. Preparation of specific polyclonal antibodies to a C-C chemokine receptor, CCR1, and determination of CCR1 expression on various types of leukocytes J Leukoc Biol 60 658-666.

3. Hornung, D , Ryan, I.P , Chao, V A., Vigne, J.L , Schnock, E.D., and Taylor, R N 1997 Immunolocalization and regulation of the chemokine RANTES in human endometrial and endometriosis tissues and cells J Clin Endocrinol Metab 82.1621-1628.

4. Khorram, O , Taylor, R.N., Ryan, I.P , Schall, T J , and Landers, D.V. 1993. Peritoneal fluid concentrations of the cytokine RANTES correlate with the severity of endometriosis Am J Obstet Gynecol 169·1545-1549.

5. Hornung, D., Bentzien, F , Wallwiener, D., Kiesel, L., and Taylor, R.N. 2001 Chemokine bioactivity of RANTES in endometriotic and normal endometrial stromal cells and peritoneal fluid Mol Hum Reprod 7 163-168.

6. Zhao, D., Lebovic, D.I , and Taylor, R N 2002 Long-term progestin treatment inhibits RANTES (regulated on activation, normal T cell expressed and secreted) gene expression in human endometrial stromal cells J Clin Endocrinol Metab 87 2514-2519

7 Altman, G.B , Gown, A M , Luchtel, D.L , and Baker, C 1999. RANTES production by cultured primate endometrial epithelial cells Am J Reprod Immunol 42:168-174
Cheret A., Le Grand R., Caufour P , Neildez O , Matheux F , Theodoro F.,

8. Medcalf R.L., Richards R.I , Crawford R.J and Hamilton J A 1986 Suppression of urokinase-type plasminogen activator mRNA levels in human fibrosarcoma cells and synovial fibroblasts by anti-inflammatory glucocorticoids EMBO J 5(9), 2217-22

9. Vaslin B., Dormont D. RANTES, IFN-gamma, CCR1, and CCR5 mRNA expression in peripheral blood, lymph node, and bronchoalveolar lavage mononuclear cells during primary simian immunodeficiency virus infection of macaques. 1999. Virology. 15;255(2):285-93.

10 Margulies B J., Hauer D.A , Clements J.E. Identification and comparison of eleven rhesus macaque chemokine receptors. 2001. AIDS Res Hum Retroviruses. 1,17(10).981-6.

11 D'Hooghe T.M., Bambra C.S., Raeymaekers B.M., De Jonge I , Lauweryns J.M., Koninckx P R. Intrapelvic injection of menstrual endometrium causes endometriosis in baboons (Papio cynocephalus and Papio anubis) 1995. Am J Obstet Gynecol.173(1) 125-34.

12 Zong L.L., Li Y L , Wang L.X , Zou J., Li J , Li T. Di Yi Jun Yi Da Xue Xue Bao. Establishment of animal models of endometriosis in rhesus monkeys 2003. 23(10) 1006-9.

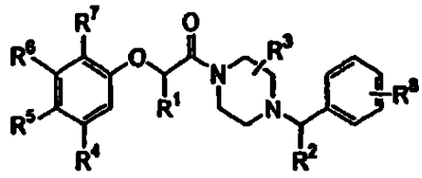
13 D'Hooghe T.M., Nugent N., Cuneo, S., Chai D., Deer, F., Debrock, S. Mwenda, J. (2001).Recombinant human TNF binding protein (r-hTBP-1) inhibits the development of endometriosis in baboons: a prospective, randomized, placebo-and drug-controlled study.Abstract for an oral presentation at the Annual Meeting of the American Socity for Reproductive Medecine, Orlando, USA October 22nd-24th.

14 Fazleabas A.T., Brudney A , Gurates B , Chai D., Bulun S 2002 A modified baboon model for endometriosis. Ann N Y Acad Sci. 955: 308-317, discussion 340-2, 396-408

15 Stoeckemann K , Hegele-Hartung C Effects of progesterone antagonists onapristone and ZK 136799 on surgically induced endometriosis in intact cycling rats Human Reproduction 1995 Dec; 10(12). 3264-71

TABLE 1

Test Compounds



Cpd #	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	K_i (nM)
1	methyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 µM
2	ethyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 µM
3	isopropyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 µM
4	propyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 µM
5	butyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 µM
6	hexyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 µM
7	H	H	H	methoxy	methoxy	methoxy	H	H	328 nM
8	H	H	H	methoxy	H	H	H	H	> 10 µM
9	H	H	H	H	methoxy	H	H	H	> 10 µM
10	H	H	methyl	methoxy	methoxy	methoxy	H	F	18 nM
11	H	H	methyl	H	Cl	H	H	F	10 nM
12	H	H	2,5-dimethyl	H	Cl	H	H	F	4 nM
13	dimethyl	H	methyl	H	Cl	H	H	F	> 10 µM

Table 2

Nr.	Compound	Ki (nM)
1	1-((phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	108
2	(*trans*)-1-((4-chlorophenylamino)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	16
3	(*trans*)-1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	11
4	(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	56
5	(*trans*)-1-((4-chloro-2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	32
6	(*trans*)-1-((4-chloro-2-hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	11
7	(*trans*)-1-((4-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	10
8	(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	15
9	1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	3
10	(2*R*,5*S*)-1-((4-chloro-3-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	3
11	(*trans*)-1-((4-chloro-2-(1-hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5
12	(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5
13	(*trans*)-1-((4-chloro-2-((ethyl)(1-methylbutyl)aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	41
14	(*trans*)-1-((4-chloro-2-(ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	2
15	1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	9
16	1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	21
17	(*trans*)-1-((4-chloro-2-(benzylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	42
18	(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	87
19	1-((4-chloro-2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	5
20	(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	7
21	(*trans*)-1-((4-chloro-2-(*iso*-propylcarbonylamino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	13
22	(*trans*)-1-((4-chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	3
23	(*trans*)-1-((4-chloro-2-(2-(methoxycarbonyl)ethylcarbonylamino)-phenoxy)-methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5

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	Compound	Ki (nM)
24	(*trans*)-1-((4-chloro-2-(methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	6
25	(2*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	1
26	(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	1
27	(*trans*)-1-((4-chloro-2-((aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	2
28	(*trans*)-1-((4-chloro-2-(1-((methyl)(ethyl)amino)ethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	18
29	(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	6
30	(*trans*)-1-((4-chloro-2-((2-aminoethyl)aminocarbonyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	9
31	1-((2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	106
32	(*trans*)-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	68
33	(2*R*,5*S*)-1-((3-hydroxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5
34	(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	31
35	1-((4-chlorophenoxy)methyl)carbonyl-2-(1-hydroxyethyl)-4-(4-fluorobenzyl)piperazine	13
36	1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut-3-enyl)-4-(4-fluorobenzyl)piperazine	172
37	1-((4-chlorophenoxy)methyl)carbonyl-3-trifluoromethyl-4-(4-fluorobenzyl)piperazine	148
38	1-((4-chlorophenoxy)methyl)carbonyl-2-(2-azidoethyl)-4-(4-fluorobenzyl)piperazine	49
39	(*trans*)-1-((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	18
40	(*trans*)-1-((4-chloro-2-(phthalimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	64
41	(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	56
42	(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	26
43	(*trans*)-1-(2-(4-chlorophenyl)-2-(methylsulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	32

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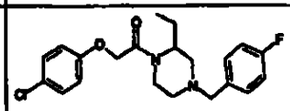
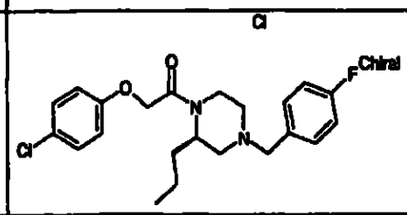
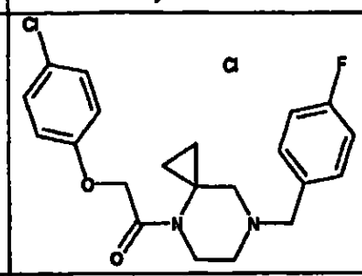
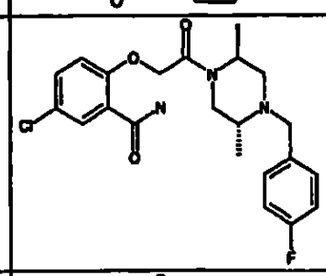
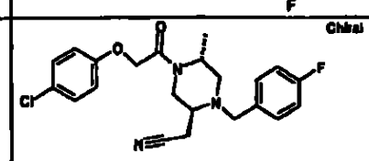
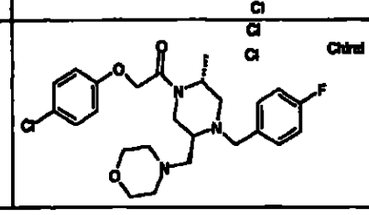
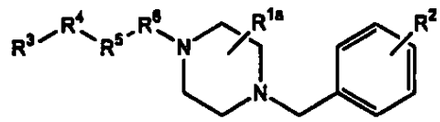
No	compound	Ki (nM)
44		15
45		75
46		74
47		3
48		38
49		109

Claims:

1 Use of a compound of the following formula (Ia):



(Ia)

for the production of a medicament for the treatment and the prevention of edometriosis in human wherein

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl) amino(C1-C8)alkyl, halo(C1-C8)alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2- C8)alkenyl, formyl, formyl(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2- C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, mercapto(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8) alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, azido(C1-C8)alkyl, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8) alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1- C8)alkyl, (C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or

naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8) alkyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (C1- C8)alkylthio(C1-C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8) alkylsulfonyl(C1-C8)alkyl, (C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy, halo(C1-C8) alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy)(C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10) cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl)amino, ((C3- C10)cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, cyano(C1-C8)alkyl, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-

C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8) alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1- C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8) alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkoxycarbonylamino(C1-C8) alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbony((C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C7-C8) alkylaminocarbonyl(C1-C8)alkyl, amidino, guanidino, ureido, mono(C1-C8) alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and

sulfur and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl,

R^3 is

a carbocylic 3- to 15-membered ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8) alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1- C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, amino(C1-C8)alkylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino, alkylcarbonylamino, (C1-C8) alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-

C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1- C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, di(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl,

aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureidoalkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mona(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

or R^3 is

a 3-15 membered heterocyclic ring system consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen,

oxygen and sulfur, substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8)alkoxy, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, amino, mono(C1- C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl(C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, monoalkylamino(C1-C8)alkyl, di(C1- C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1- C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido;

R^4 is

-O-, -N(R^7)-, -C(R^8)$_2$- or a bond;

R^5 is

an (C1-C8) alkylene chain or an (C1-C8) alkylidene chain, or, if R^4 is a bond, R^5 is an (C1-C8) alkylidene chain optionally substituted by (optionally substituted phenyl or naphthyl) or -N(R^7)$_2$;

or R^4 and R^5 together are –HC=CH-

R^6 is

-C(O)-, -C(S)-, $-CH_2-$ or a bond;

each R^7

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkylcarbonyl, (C1-C8) alkylcarbonyl(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1- C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8)alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) aminoalkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl,

mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl;

provided that when R^4 is $-N(R^7)-$, R^3 cannot be a heterocyclic ring system containing 4-8 members consisting of carbon atoms and only one nitrogen atom; and provided that when R^4 is $-C(R^8)_2$ or a bond, R^3 cannot be a bridged saturated heterocyclic ring system containing 4-6 members consisting of carbon atoms and two nitrogen atoms, and as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof

2 The compound of Claim 1 wherein:

R^3 is

a 3- to 15- membered carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8) alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino,

amino(C1-C8)alkylamino, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, amino, ((C3-C10)cycloalkyl(C1- C8)alkyl) amino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, di(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl,

aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon

atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

3. The compound of Claim 2 wherein:

R^4 is

-O-, -N(R^7)- or -C(R^8)-;

R^5 is

an (C1-C8)alkylene chain,

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl, and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8) alkyl,

((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8)alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbony4(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl.

4. The compound of Claim 3 wherein·

R^4 is

-O-;

R^5 is

methylene, and

R^6 is

-C(O)-

5. The compound of Claim 4 wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2- C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-

C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo,

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalky(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-CS)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)

sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy) carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl) ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

6. The compound of Claim 5 selected from the group consisting of the following compounds:

(2*S*)-1-((4-chlorophenoxy)methyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine;

1-((phenoxy)methyl) carbonyl-2-ethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl) -1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(methoxymethyl) piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-((acetylamino)methyl)piperazine;

1-((4-chlorophenoxy) methyl)carbonyl-2-(2-((4-fluorobenzyl)amino)ethyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((methyl)amino)ethyl)-4- (4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl- 2-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methyl-5-methylpiperazine;

4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(methoxycarbonyl)methylpiperazine,

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-3-((methoxy)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-(methoxy) ethyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl)piperazine,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxypropyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxybut-4-ynyl)piperazine,

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine ;

1-((4-chlorophenoxy)methyl)carbonyl-3- (2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine,

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine;

(2*S*,5*R*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(2*S*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine,

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(2-methylthio)ethylpiperazine,

(2*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy)methylpiperazine,

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((2- hydroxyethyl)thio)methyl)piperazine,

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(*N'*-(ethoxycarbonylmethyl) ureido) methyl)piperazine,

(2*R*,5*S*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((amino)carbonyloxy)methyl-4-(4-fluorobenzyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-((acetyl)methyl)piperazine,

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-5-(1-hydroxybutyl)piperazine;

(2*R*,5 *S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((diethylamino)methyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((dimethylamino)methyl)piperazine,

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine;

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1- yl)methyl)piperazine;

(*cis*)-1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine,

1-((phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine,

1-((2-(acetylamino)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxypropyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut- 3-enyl)-4-(4-fluorobenzyl)piperazine,

1-((4-chlorophenoxy)methyl) carbonyl-3-trifluoromethyl-4-(4-fluorobenzyl)piperazine, and

(*trans*)-1-((4-chloro-2-((4-(2,5-di(trifluoromethyl)phenylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

7. The compound of Claim 5 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8) alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3- C10)cycloalkylcarbonylamino, (optionally

substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally

substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

8. The compound of Claim 7 selected from the group consisting of the following compounds:

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine,

1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine,

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

(2*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-propylpiperazine,

4-(4- fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl)spiro[cyclopropane-1, 2'-piperazine];

1-((4-chlorophenoxy)methyl)carbonyl-2- hydroxymethyl-4-(4-fluorobenzyl)piperazine,

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(2-(methoxy)ethyl)piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2-methylpropyl)amino)ethyl) -4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine,

1-((4- chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5-methylpiperazine;

(2*R*)-1-((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine,

(2*S*)-1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(hydroxymethyl) piperazine,

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxyethyl)piperazine,

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(((methyl)ureido)methyl)piperazine,

(2*R*,3*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,3-dimethylpiperazine,

(*cis*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5-methylpiperazine;

(2 *R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5((hydroxy)methyl)piperazine;

(2*R*,5*R*) -4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-((methoxy)-methyl)piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine,

(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxyethyl)piperazine;

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyprop-3-enyl)piperazine,

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine,

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl) piperazine,

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl)piperazine;

(3*S*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3,5-dimethylpiperazine;

1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((ethyl)(1-methylbutyl)aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro-2- aminophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (benzylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*iso*-propylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(4-nitrophenyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(4-methylphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (acetylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(1-(phenylsulfonyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(1- ((methyl)(ethyl)amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (dimethylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(2*R*)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(oxazol-2- ylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-(morpholin-4-ylmethyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(trans)-1- ((4-bromo-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-methoxycarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro- 2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans)*-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine,

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(*trans*)-1-((4-methyl-2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-methyl-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((5-nitro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- nitro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((5- methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-acetyl-4,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl)piperazine;

(*trans*)-1-((4- methyl-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((3-chloro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chlorophenoxy)methyl)carbonyl-2- (2-azidoethyl)-4-(4-fluorobenzyl)piperazine,

(*trans*)-1- ((4-chloro-2-(phthalimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (maleimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((4-(benzylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2,3, 4-trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(2,6-difluorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(ethenylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(cyclopropylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(cyclopentylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((furan-2-yl)carbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((*N'*-(3-methoxyphenyl)ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((*N'*-(methoxycarbonylmethylcarbonyl)-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2- methoxycarbonylethyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl)aminocarbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(3-trifluoromethyl-4-fluorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(4- methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(3-chlorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(4- fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(2,3-difluorophenylcarbonyl) glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(*N'*-(2,4-difluorophenylcarbonyl)glycinamido)phenoxy)methyl) -carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((ethoxycarbonylmethylcarbonyl) aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(3-chloropropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'* -(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)-methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((3-fluorophenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(*N'*-(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(2*S*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4- chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

9 The compound of Claim 7 wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl and hydroxy(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)

alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl

10. The compound of Claim 9 selected from the group consisting of the following compounds.

(*trans*)-1-((4-chloro-3-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(2*S*,5*R*)-1-((4-bromo-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((3-hydroxy-5-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2 *S*,5*R*)-1-((4-nitro-3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(2R)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl) piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine,

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(2*R*,5*S*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine;

(2*R*,6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,6-dimethylpiperazine;

(*trans*)-1-((4-chloro-2- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(1-hydroxyethyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino- 4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine,

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(2- (methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(2*R*)-1-((4-chloro-2-(glycinamido) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-ethylureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-amino-5-nitrophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt,

(*trans*)-1-((4-chloro-2-(((ethyl)amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(((diethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(((cyclopropyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (((dimethyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((methyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-methylpiperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(1- (methylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(methylsulfonyl) (methyl)aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(imidazol-1-ylmethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-(triazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(tetrazol-1-ylmethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((morpholin-4-yl)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1-((4- chloro-2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4- chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(2*R*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1- ((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2- aminoethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((4- aminocarbonyloptionally substituted phenyl)aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(hydroxyamidino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(*N'*-(methoxymethylcarbonyl)glycinamido)phenoxy) methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, and

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonylaminocarbonyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine

11 The compound of Claim 9 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4-position with chloro and at the 2-position by aminocarbonyl, ureido, or glycinamido, namely, the compound selected from the group consisting of the following compounds

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-(ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(2*R*, 5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine, and

(2*R*,5*S*)-1-((4- chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine

12 The compound of Claim 9 wherein the most preferred compound is:

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine,

13 The compound of Claim 3 wherein:

R^4 is

-N(R^7)-,

R^5 is

methylene,

R^6 is

-C(O)-, and

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl.

14 The compound of Claim 13 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8)

alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1-C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo,

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1- C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8)alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)

alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy) carbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group

of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) (C1-C8)alkyl.

15 The compound of Claim 14 wherein

R^{18} is

one or more substituents independently selected from the group consisting of (C1- C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8) alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl) (c1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(c1- C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-

C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(c1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl

16 The compound of Claim 15 wherein:

R^{19} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8) alkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (3C-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8) alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl

17. The compound of Claim 16 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4- position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido.

18 The compound of Claim 17 selected from the group consisting of the following compounds.

(*trans*)-1-((4-chlorophenylamino)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro- 2-(aminocarbonyl)phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine, and

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl- 4-(4-fluorobenzyl)piperazine.

19 The compound of Claim 3 wherein

R^4 is

$-C(R^6)_2-$;

R^5 is

methylene;

R^6 is

-C(O)-; and

each R^8

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, and di(C1-C8)alkylamino(C1- C8)alkyl

20 The compound of Claim 19 wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)

alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo,

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-

C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8) alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl) aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, di(C1-C8) alkylaminocarbonyl(C1-C8) alkyl, hydroxyamidino, ureido, mono(C1-C8) alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur

and (3-15membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl

21 The compound of Claim 20 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro,

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8) alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-

C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl; (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

22 The compound of Claim 21 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8)alkyl,

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8) alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1- C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl

23. The compound of Claim 22 wherein:

R^2 is

4- fluoro,

R^3 is

phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido, and

one R^8 is

hydrogen and the other R^8 is selected from the group consisting of amino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl)

carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, and amino(C1-C8)alkyl

24 The compound of Claim 23 selected from the group consisting of the following compounds

(*trans*)-1-(2-(4-chlorophenyl)-3- (methylsulfonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2-(methylsulfonylamino)ethyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4- chlorophenyl)-2-(acetylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-2- (amino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(ureido)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4- chlorophenyl)-3-(ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4- chlorophenyl)-3-(*t*-butoxycarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4- chlorophenyl)-2-((ethoxycarbonylmethylcarbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'-iso*-propylureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'*-(2-chloroethyl)ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((2-nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4- chlorophenyl)-2-((2,4-dinitrophenyl)sulfonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4- chlorophenyl)-2-(cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)- 2-((2-cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3- ((2-methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (*t*-butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (ethyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl) ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

25 The compound of Claim 1 wherein·

R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8) alkyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl) sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8) alkoxy, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino,

mono(optionally substituted phenyl or naphthyl) (C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1-C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido

26. The compound of Claim 25 wherein

R^4 is

-O-, - N(R^7)- or -C(R^8)-,

R^5 is

an (C1-C8) alkylene chain,

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl, and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl

27 The compound of Claim 26 wherein

R^4

is -O-,

R^5

is methylene, and

R^6

is -C(O)-.

28. The compound of Claim 26 wherein

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl, and

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo

29 The compound of Claim 28 wherein R^3 is selected from the group consisting of azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperazinyl, 4- piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl,

tetrahydrofuryl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone

30. The compound of Claim 29 wherein R^3 is benzopyranyl, benzopyranonyl, benzfuranyl, benzofuranonyl, quinolinyl, indolyl, indolinyl, oxazolyl, imidazolyl, or benzothienyl

31. The compound of Claim 30, namely, (*trans*)-1-((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

32 The compounds

(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oXopropenyl]- phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oxopropenyl] phenyl)-methanesulfonamide,

(5-Chloro-2-[(E)-3-[(2R, 5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-methanesulfonamide,

(5-Chloro-2- {(E)-3-[4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-phenyl)-acetic acid methyl ester,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-benzoic acid,

(5-chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-urea,

(5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxopropenyl}-4-trifluoromethoxy-phenyl)-urea,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oXo-propenyl}-4-methoxy-benzoic acid methyl ester

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-propionic acid,

(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4- (4-chloro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(3, 4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acrylic acid,

N-[(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-methanesulfonamide,

N- (5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzoyl)-methanesulfonamide,

N- [(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-C,C,C-trifluoro-methanesulfonamide,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-oxo-acetic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-acetic acid,

2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-2-methyl-propionic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-difluoro-acetic acid

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide

N-[5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]phenyl-trifluoromethanesulfonamide,

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]- benzenesulfonamide

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl) phosphonic acid monoethyl ester,

5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R5S)-2,5-dimethYl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonamidic acid

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester;

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid methyl ester,

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid methyl ester,

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-bromo-2-[2-[(2*R*)-4-[(5-chloro-2-thienyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-4-(dimethylamino)-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid,

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid,

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid,

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid,

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid,

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid,

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid,

5-chloro-4-ethoxy-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid,

4-amino-5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid,

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid,

4-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-5-methylbenzoic acid

for the production of a medicament for the treatment and the prevention of edometriosis in human

33. A pharmaceutical composition useful in treating endometriosis in a human female in need of such treatment, which composition comprises a therapeutically effective amount of a compound according to claim 1

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Fig. 1

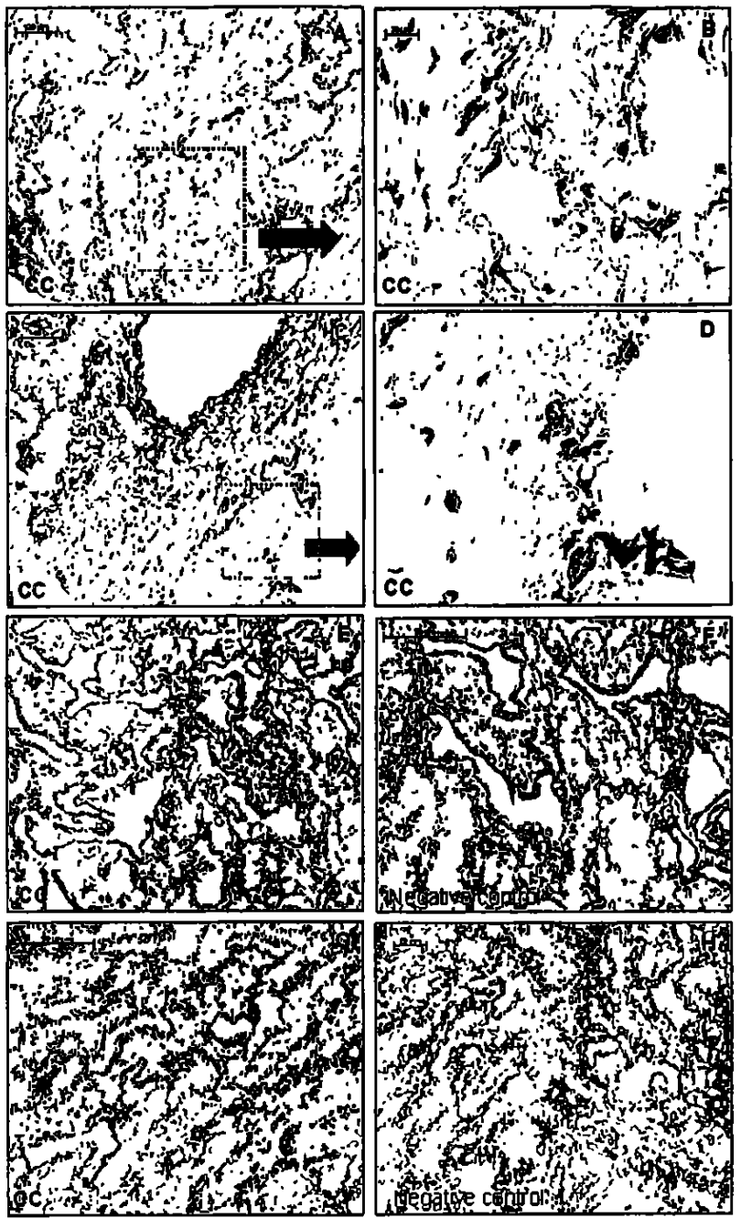


Fig. 2

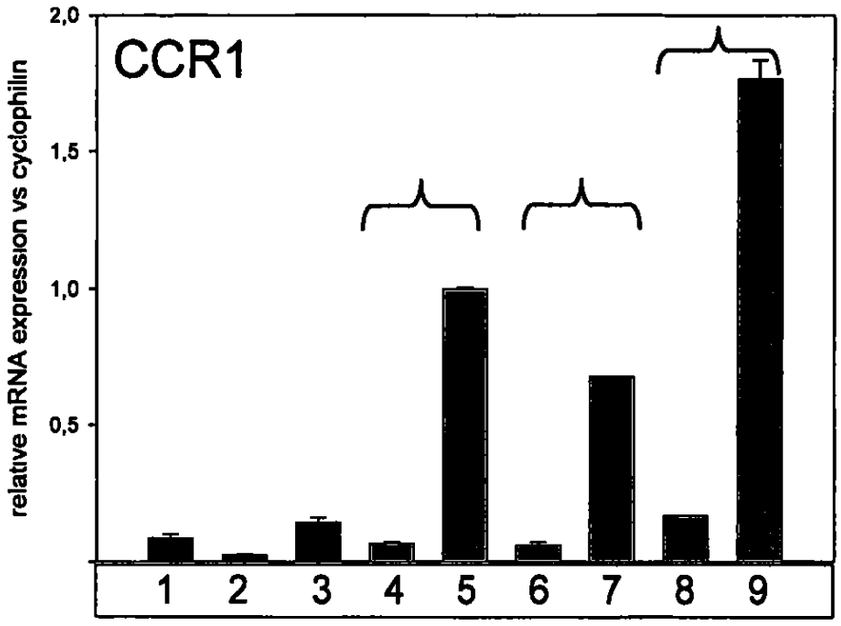

CCR1
relative mRNA expression vs cyclophilin
2,0
1,5
1,0
0,5
1
2
3
4
5
6
7
8
9

Fig. 3

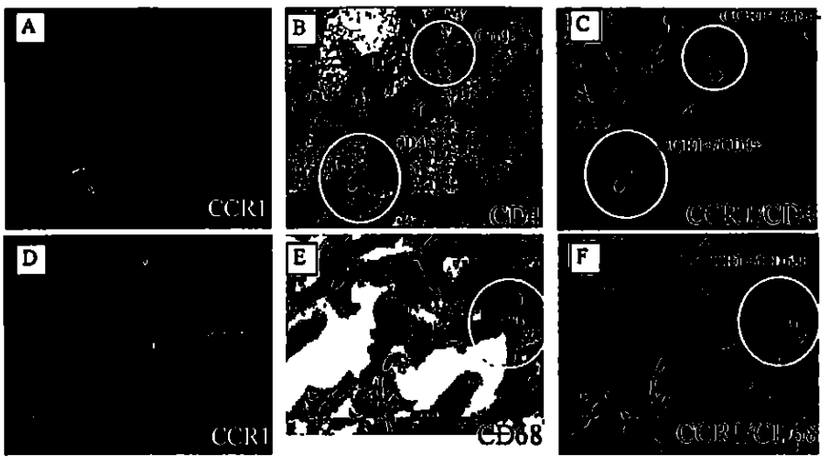


Fig. 4

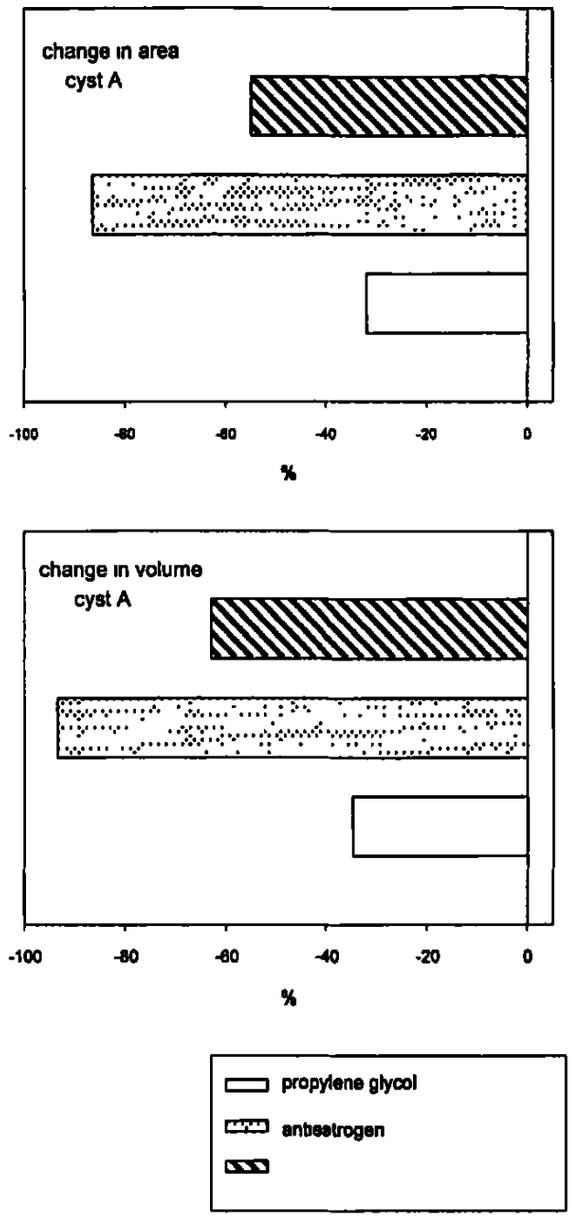

change in area
cyst A
-100
-80
-60
-40
-20
0
%
change in volume
cyst A
-100
-80
-60
-40
-20
0
%
propylene glycol
antiestrogen

Fig. 5a

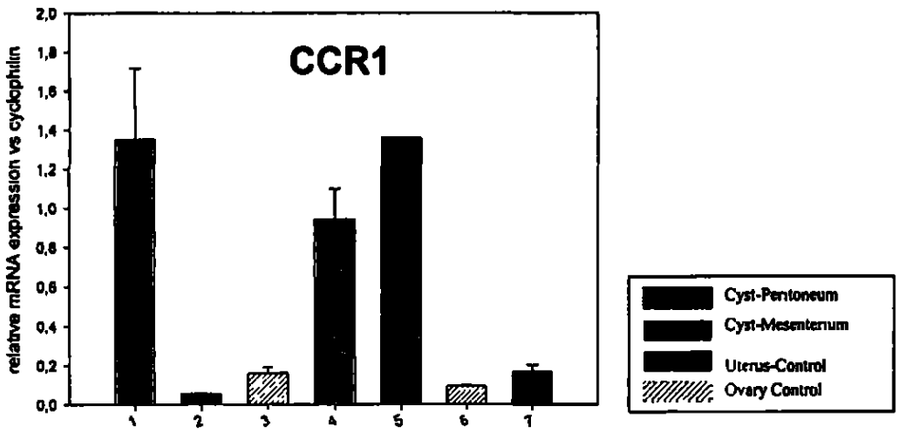

CCR1
relative mRNA expression vs cyclophilin
2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
1
2
3
4
5
6
7
Cyst-Peritoneum
Cyst-Mesenterium
Uterus-Control
Ovary Control

Fig. 5b

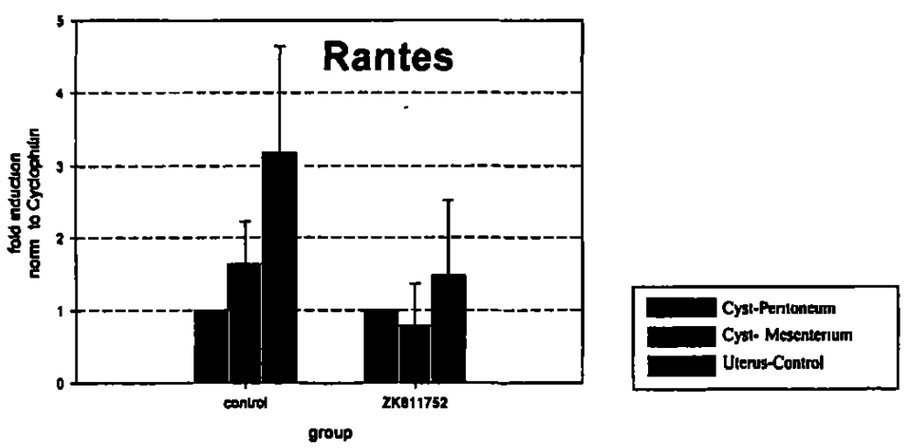
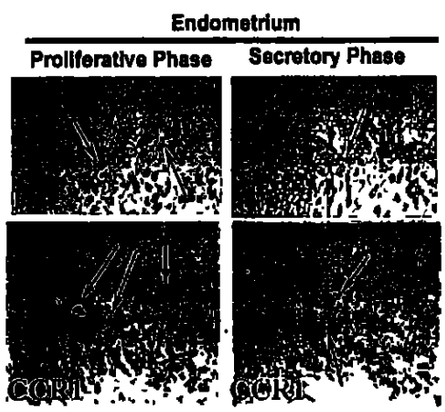

Rantes
fold induction norm to Cyclophilin
5
4
3
2
1
0
control
ZK811752
group
Cyst-Peritoneum
Cyst- Mesenterium
Uterus-Control

Fig. 6a

Number of CCR1 stained cells during menstrual

	PP	SP	SP
Endometrium	10	[illegible]	[illegible]
Grafts	66	101	[illegible]

Fig. 6b



PP = Proliferative Phase
SP = Secretory Phase
SP = Secretory Phase

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(71) **Solicitante (para todos los estados designados con excepción de US): SCHERING AKTIENGESELLSCHAFT** [DE/DE]; Mullerstrasse 178, 13353 Berlin (DE) **HORUK, Richard** [US/US], 3410 Silver Springs Court, Lafayette, CA 94549, California CA 94549 (US)
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(81) **Estados designados** (en la medida en que no se indique lo contrario, para cada tipo de protección nacional disponible) AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
(84) **Estados designados** (en la medida en que no se indique lo contrario, para cada tipo de protección regional disponible) Patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Patente euroasiatica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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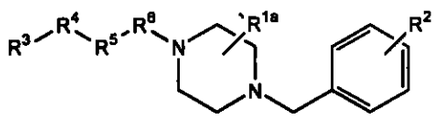
(54) Título: **Piperazinas derivadas de urea para el tratamiento de la endometrosis**

(57) Resumen



(Ia)

Uso de un compuesto de la siguiente formula (Ia) para la producción de un medicamento para el tratamiento de la endometrosis en seres humanos en donde el tratamiento comprende administrar a un humano de sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de dicho compuesto

WO 2005/079769 PCT/EP2005/002036

PIPERAZINAS DERIVADAS DE UREA PARA EL TRATAMIENTO DE LA ENDOMETROSIS

Campo de la invención

La presente invención se refiere a derivados de piperazina y sus sales aceptables para uso farmacéutico, que inhiben la actividad de las quimioquinas, MIP-1α y RANTES que son antagonistas del Receptor 1 de Quimioquina Humana "C-C" (CCR1) que de esa manera son útiles para el tratamiento de la endometrosis. La misma también se refiere a composiciones farmacéuticas que contienen los derivados o sus sales aceptables para uso farmacéutico, y a métodos para su uso

ANTECEDENTES DE LA INVENCIÓN

Los receptores de quimioquina se expresan en los leucocitos y procesan las señales que siguen a la unión de la quimioquina debido a lo cual dichas señales se transducen eventualmente en la migración de los leucocitos hacia la fuente de la quimioquina o su activación. Por lo tanto, al regular la migración y activación de los leucocitos desde la sangre periférica hacia sitios extravasculares en los órganos, piel, articulaciones o tejido conectivo, las quimioquinas desempeñan un papel crítico en el mantenimiento de las defensas del huésped así como en el desarrollo de la respuesta inmune.

Se ha descubierto que el Receptor 1 de Quimioquina

Humana "C-C" (CCR1) responde a varias quimioquinas CC humanas en una variedad de ensayos que incluyen movilización de calcio, inhibición del aumento de adenilato ciclasa en la acidificación extracelular y quimiotaxis El rango de quimioquinas que se puede señalar mediante el CCR1 es amplio e incluye MIP-1 alfa, RANTES, MCP-3, entre otras. Todos dichos ligandos son potentes agonistas para el CCR1 humano (EC50<10nM). Además, el CCR1 humano también es capaz de unirse a MIP-1ß y MCP-1 humana con baja afinidad (>100nM) pero ninguno de ambos ligandos es capaz de señalizar (1) Mediante el uso de anticuerpos policlonales para CCR1, se ha descubierto que el receptor se expresa en monocitos y linfocitos pero no en neutrófilos (2).

Se ha informado que las moléculas que inhiben la actividad del CCR1 aportan beneficios para tratar enfermedades como por ejemplo esclerosis múltiple, artritis reumatoide y otras enfermedades inflamatorias crónicas

La endometrosis es una enfermedad inflamatoria crónica, que se caracteriza por la implantación y el crecimiento de tejido endometrial fuera de la cavidad uterina(3). Se describe clásicamente como la presencia de tejido endometrial (epitelio glandular y estroma) fuera de la cavidad uterina. La endometrosis es una enfermedad crónica benigna, que afecta durante su vida reproductiva al 15-20% de todas las mujeres.

Los síntomas de la endometrosis son dolor pélvico crónico, dismenorrea progresiva, dispareunia así como infertilidad.

El tratamiento de la endometrosis incluye la resección quirúrgica y/o la medicación con agentes hormonales como por ejemplo agonistas de la hormona liberadora de gonadotropina (GnRH) y andrógenos. Sin embargo, la medicación a largo plazo con agentes hormonales no es deseable debido a los efectos secundarios como por ejemplo trastornos menopáusicos (calores), hemorragia genital y desmineralización ósea.

Frecuentemente el control clínico de la endometrosis es muy difícil y la proporción de recurrencia es alta después de discontinuar la medicación

El papel del CCR1 y sus ligandos en la endometrosis surge del hecho que la menstruación retrógrada se postula como el evento iniciador en la patogénesis de la enfermedad. Además, la misma es acompañada por una infiltración intraperitonial de macrófagos y células T en las lesiones endometriósicas. El reclutamiento de dichos leucocitos dentro de las lesiones endometriales se inicia por la producción local de quimioquinas. El ejemplo más notable de quimioquina CC, RANTES (3-7), es, entre otras, un ligando para los receptores de quimioquina CCR1, y CCR5. La expresión de RANTES está sensibilizada en las lesiones endometriósicas y en el fluido peritoneal proveniente de pacientes con endometrosis. En

comparación con otras quimioquinas, RANTES desempeña un papel importante en la patogénesis de la endometrosis.

Trabajos Relacionados

Los derivados piperazina del tipo similar a los compuestos de la invención se conocen en la literatura como útiles para una variedad de indicaciones farmacéuticas, en particular como agentes cardiotónicos, neurotrópicos o antiinflamatorios. Por ejemplo, la solicitud publicada de patente europea 0 702 010 (Adir) describe ciertos derivados de piperazina como útiles como depresores del sistema nervioso central y en el tratamiento de la enfermedad de Alzheimer y otras enfermedades de origen inmunológico, como por ejemplo artritis y peristaltismo intestinal La solicitud publicada de patente europea 0 655 442 (Fujisawa) describe derivados de piperazina similares como antagonistas de taquiquinina que son útiles para tratar enfermedades inflamatorias como por ejemplo artritis reumatoide y osteoartritis Una solicitud de patente publicada checa, 260089, y un artículo relacionado, Valenta, V. Et *al* , *Collection Chem Commun.* (1987), Vol. 52, pp. 3013-3023, revela derivados de piperazina como potenciales agentes neurotrópicos y cardiovasculares. La solicitud publicada de patente europea 0 252 422 (Mitsubishi) y la solicitud publicada de patente alemana 3614363 (Hoechst) describe derivados de piperazina que son útiles como agentes cardiotónicos. La solicitud publicada de

patente europea 0 190 685 (G. D. Searle) describe derivados de piperazina que bloquean la vía metabólica de la 5-lipooxigenasa de la cascada del ácido araquidónico, y por lo tanto son útiles en el tratamiento de reacciones alérgicas y de hipersensibilidad e inflamación La solicitud publicada de patente PCT, WO 96/34864 (Schering Plough) revela derivados de piperazina útiles como antagonistas de neuroquinina.

La solicitud publicada de patente europea 1 254 899 (Schering AG) revela los derivados de piperazina comprendidos en la presente solicitud para el tratamiento de un trastorno inflamatorio.

La solicitud de patente PCT WO 02/36581 (Schering AG) revela también derivados de piperazina comprendidos en la presente solicitud para el diagnóstico de la enfermedad de Alzheimer.

Todas las referencias anteriores se incorporan aquí en su totalidad como referencia.

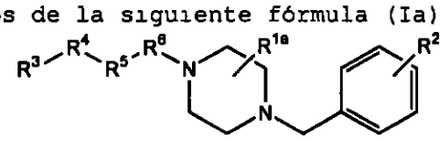
Ninguna de las referencias anteriores describe los derivados de piperazina comprendidos en la presente solicitud para el tratamiento de la endometrosis en mujeres, donde dichos derivados de piperazina son antagonistas de Receptor 1 de Quimioquina Humana "C-C" (CCR1).

RESUMEN DE LA INVENCIÓN

Esta invención se relaciona con el uso de un compuesto de la siguiente fórmula (Ia) o su sal aceptable para uso

farmacéutico para el tratamiento y prevención de la endometrosis en seres humanos en donde el tratamiento comprende administrar a un humano de sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de dicho compuesto

De acuerdo con esto, en un aspecto, esta invención provee compuestos de la siguiente fórmula (Ia)



(Ia)

en donde·

R^{1a} es

uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por oxo, halo, alquilo, cicloalquilo, cicloalquilalquilo, cicloalquilaminoalquilo, (cicloalquilalquil)aminoalquilo, haloalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, formilo, formilalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, mercaptoalquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, (alcoxi)aralquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, hidroxialquiltioalquilo, aminoalquilo monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo,

azidoalquilo, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, (alcoxicarbonilalquil) ureidoalquilo, alcoxicarbonilaminoalquilo, hidroxialquilaminoalquilo, ariloxialquilcarboniloxialquilo, alcoxialquilcarboniloxialquilo, aralcoxialquilcarboniloxialquilo, alquilcarbonilo, alquilcarbonilalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, aralquilcarbonilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, arilsulfonilo, heterociclilo y heterociclilalquilo;

R^2 es

uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, alquilo, mercapto, mercaptoalquilo, alquiltio, alquilsulfinilo, alquilsufonilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, alcoxi, ariloxi, haloalquilo, formilo, formilalquilo, nitro, nitroso, ciano, aralcoxi, haloalcoxi, cicloalquilo, cicloalquilalquilo, (hidroxi)cicloalquilalquilo, cicloalquilamino, cicloalquilaminoalquilo, (cicloalquilalquil)amino, (cicloalquialquil)aminoalquilo, cianoalquilo,

alquenilo, alquinilo, arilo, aralquilo, aralquenilo, hidroxialquilo, (hidroxi)aralquilo, hyaroxialquiltioalquilo, hidroxialquenilo, hidroxialquinilo, alcoxialquilo, (alcoxi)aralquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, hidroxialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, (alquilcarbonil) (alquil)aminoalquilo, alcoxicarbonilamino, (alcoxicarbonil)(alquil)amino, alcoxicarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, alquilcarbonilalquilo, arilcarbonilo, arilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, alcoxialquilcarboniloxialquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, amino-carbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, amidino, guanidino, ureido, monoalquilureido, dialquilureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, heterociclilo y heterociclilalquilo;

R^3 es

un sistema de anillo carbocíclico sustituido por uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, alquilo, mercapto, mercaptoalquilo, alquiltio, alquilsulfinilo, alquilsufonilo, arilsulfonilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, alcoxi, hidroxialcoxi, ariloxi, haloalquilo, formilo, formilalquilo, nitro, nitroso, ciano, aralcoxi, haloalcoxi, aminoalcoxi, cicloalquilo, cicloalquilalquilo, (hidroxi) cicloalquilalquilo, cicloalquilamino, cicloalquilaminoalquilo, cianoalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, hidroxialquilo, (hidroxi) aralquilo, (monoalquilamino) aralquilo, (hidroxialquil)hioalquilo, hidroxialquenilo, hidroxialquinilo, alcoxialquilo, (alcoxi)aralquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, aminoalquilamino, heterociclilamino, (cicloalquilalquil)amino, alquilcarbonilamino, alcoxicarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, (alcoxicarbonil)(alquil)amino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, di-

alquilaminoalquilo, hidroxialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, (cicloalquialquil) aminoalquilo, alcoxicarbonilaminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil)(alquil)aminoalquilo, heterociclilaminoalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, arilcarbonilo, aralquilcarbonilo, (hidroxialcoxi)carbonilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, alcoxialquilcarboniloxialquilo, dialquilaminocarboniloxialquilo, alquilcarbonilalquilo, arilcarbonilalquilo, aralquilcarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, (aminocarbonilalquil) aminocarbonilo, (monoalquilaminocarbonilalquil) aminocarbonilo, (carboxialquil) aminocarbonilo, (alcoxicarbonilalquil)aminocarbonilo, (aminoalquil) aminocarbonilo, (hidroxialquil)aminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, amidino, hidroxiamidino, guanidino, ureido, monoalquilureido, monoarilureido, monoaral-

quilureido, monohaloalquilureido, (monoalquil)(monoaril)ureido, dialquilureido, diarilureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil) ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil) glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil)glicinamido, (alcoxicarbonilamino-alquilcarbonil)glicinamido arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil)glicinamido, (monoaralquilaminocarbonil)(alquil)gli-cinamido, (monoarilaminocarbonil) glicinamido, (monoarilaminocarbonil)(alquil)glicinamido, glicinamidoalquilo, alaninamido, monoalquilalaninamido, alaninamidoalquilo,heterociclilo y heterociclilalquilo,

o R^3 es

un sistema de anillo heterocíclico sustituido por uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por hidrógeno, hidroxi, halo, alquilo, alquilsufonilo, arilsulfonilo, alcoxi, hidroxialcoxi, haloalquilo, formilo, nitro, ciano, haloalcoxi, alquenilo, alquinilo, arilo, aralquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino,

alquilcarbonilamino, alcoxicarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, (alcoxicarbonil)(alquil)amino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil) aminoalquilo, alcoxicarbonilaminoalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, arilcarbonilo, aralquilcarbonilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, guanidino, ureido, monoalquilureido, ureidoalquilo, monoalquilureidoalquilo, y glicinamido,

R^4 es

-O-, $-N(R^7)-$, $-C(R^8)_2-$ o un enlace;

R^5 es

una cadena alquileno o una cadena alquilideno, o, si R^4 es un enlace, R^5 es una cadena alquilideno que se sustituye opcionalmente por arilo o $-N(R^7)_2$,

o R^4 y R^5 juntos son un -CH=CH-

R^6 es

-C(O)-, -C(S)-, $-CH_2-$ o un enlace,

cada R^7

se selecciona en forma independiente entre el grupo formado por hidrógeno, alquilo, arilo, aralquilo, alquilcarbonilo, alquilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, y alcoxicarbonilo; y

cada R^8

se selecciona en forma independiente entre el grupo formado por hidrógeno, alquilo, arilo, aralquilo, hidroxi, alcoxi, hidroxialquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, alquilcarbonilamino, cicloalquilcarbonilamino, cicloalquilalquilcarbonilamino, alcoxicarbonilamino, alquilsulfonilamino, arilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, aralquilcarbonilamino, (aralquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, cicloalquilcarbonilaminoalquilo, alcoxicarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, aralquilcarbonilaminoalquilo, heterociclilcarbonilaminoalquilo, (aralquilcarbonil)(alquil)aminoalquilo, arilsulfonilamino, alquilsulfonilaminoalquilo, ureido, monoalquilureido, monohaloalquilureido, dialquilureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monohaloalquilureidoalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, carboxialquilo, alcoxicarbonilalquilo,

aminocarbonilalquilo, monoalquilaminocarbonilalquilo, y dialquilaminocarbonilalquilo,

con la salvedad de que cuando R^4 es $-N(R^7)-$, R^3 no puede ser un sistema de anillo heterocíclico de 4-8 miembros que consiste de átomos de carbono y sólo un átomo de nitrógeno; y con la salvedad de que cuando R^4 es $-C(R^8)_2$ o un enlace, R^3 no puede ser un sistema de anillo heterocíclico saturado con puente de 4-6 miembros que consiste de átomos de carbono y dos átomos de nitrógeno, y como único estereoisómero o una mezcla de los mismos; o una sal aceptable para uso farmacéutico de los mismos. La salvedad tiene la finalidad de excluir los compuestos revelados en el documento del arte previo WO 96/34864.

La solicitud de patente WO2004/037796 en su totalidad es se incorpora por referencia a la presente solicitud Algunas formas de realización ventajosas de acuerdo con la presente invención son el compuesto de acuerdo con la fórmula general I, II, IIa y III según se define en WO2004/037796 para la producción de un medicamento para el tratamiento y prevención de la endometrosis. Algunas realizaciones particularmente favorables de la presente invención son los siguientes compuestos según se informan en WO2004/037796·

(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpiperazin-1-il]-3-oXopropenil]- fenil)-urea,

N-(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpipe-

razin-1-il]-3- oxopropenil] fenil)-metansulfonamida, (5-Cloro-2-[(E)-3-[(2R, 5S)-4-(4-fluorobencil)-2, 5-dimetilpiperazin-1-il]-3- oxopropenil]-fenil)-urea, N-(5-Cloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobencil)-2,5-dimetil-piperazin-1-il]-3-oxopropenil]-fenil)-metansulfonamida, metiléster de ácido (5-Cloro-2- {(E)-3-[4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxo-propenil}-fenil)-acético, ácido 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il}-3-oxo-propenil}- benzoico, (5-cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxo-propenil}-4-metoxi-fenil)-urea, (5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxopropenil}-4-trifluorometoxi-fenil)-urea, 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oXo-propenil}-4-metoxi-benzoico metiléster de ácido.

La solicitud de patente WO03/035627 en su totalidad se incorporan por referencia a la presente solicitud. Algunas formas de realización ventajosas de acuerdo con la presente invención son los compuestos bajo la fórmula general 1 según se define en la reivindicación 1 de WO03/035627 para el tratamiento y prevención de la endometrosis. Algunas realizaciones particularmente favorables de la presente invención son los siguientes compuestos según se informan en WO03/035627.

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)- (2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- propiónico,

ácido (5-Cloro-2-{2-[4-(3,4-difluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Cloro-2-{2-[4-(4-cloro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Cloro-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Cloro-2-{2-[4- (4-cloro-bencil)- (2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Cloro-2-{2-[4-(3, 4-difluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acrílico,

N-[(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acetil]-metansulfonamida,

N- (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R, 5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-benzoil)-metansulfonamida,

N- [(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acetil]-C,C,C-trifluoro-metansulfonamida,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-oxo- acético,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)- acético,

ácido 2-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il-2-oxo-etoxi}-fenoxi)-2-metil- propiónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)-difluoro-acético

(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfonamida

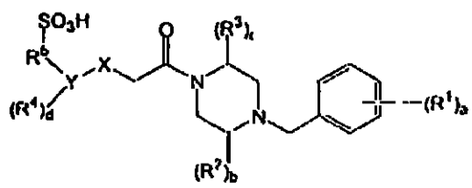
La solicitud de patente WO01/72728 en su totalidad se incorpora por referencia a la presente solicitud. Algunas formas de realización ventajosas de acuerdo con la presente invención son los compuestos bajo la fórmula general 1 según se define en la página 2 de WO01/72728 según publicada para el tratamiento y prevención de la endometrosis. Algunas realizaciones particularmente favorables de la presente invención son los siguientes compuestos según se informan en

WO01/72728:

N-[5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]fenil-trifluorometansulfonamida,

5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-bencensulfonamida.

La solicitud de patente WO02/102787 en su totalidad se incorporan por referencia a la presente solicitud Algunas



formas de realización ventajosas de acuerdo con la presente invención son los compuestos de la fórmula I- WO02/102787

(I- WO02/102787)

o sus sales aceptables para uso farmacéutico y prodrogas; en donde

a = 0, 1, 2, 3, 4 o 5; b = 0, 1 o 2, c = 0, 1 o 2; d = 0, 1,2, 3 o 4;

X es -O-, -S-, -CH2- o -NR6-

Y es (C6-C10) arilo, o (C2-C9) heteroarilo,

cada R1 se selecciona en forma independiente entre el grupo formado por: H-, HO-, halo-, (C1-C8) alquil- opcionalmente sustituido con 1-3 átomos de flúor, (C1-C8)

alquil-O- en donde el grupo alquilo es opcionalmente sustituido con 1-3 átomos de flúor, HO-(C1-C8) alquil-, NC-,H2N-,H2N-(C1-C8) alquil-, HO-(C=O)-, (C1-C8)alquil-(C=O)-, (C1-C8)alquil-(C=O)-(C1-C8)alquil-, H2N-(C=O)-, H2(C=O)-(C1-C8) alquil-,

cada R2 y R3 se selecciona en forma independiente entre el grupo formado por: H-, oxo, (C1-C8) alquil- opcionalmente sustituido con 1-3 átomos de flúor, (C1-C8) alquil-, (C6-C10) aril-, (C6-C10)aril-(C1-C8)alquil-, HO-(C1-C8)alquil-, (C1-C8)alquil-O-(C1-C8)alquilo, H2N-(C1-C8)alquilo, (C1-C8)alquil-NH-(C1-C8)alquil-, [(C1-C8)alquil]2N-(C1-C8)alquil-, (C2-C9)heterociclil-(C1-C8)alquilo, (C1-C8)alquil-(C=O)-NH-(C1-C8)alquil-, (C1-C8)alquil-O-(C=O)-NH-(C1-C8)alquilo, H2N-(C=ONH-(C1-C8)alquilo, (C1-C8)alquil-SO2-NH-(C1-C8)alquilo, (C2-C9)heteroaril-(C1-C8)alquilo, H2N-(C=O)-,H2N- (C=O)-(CI-C8) alquil-;

cada R4 se selecciona en forma independiente entre el grupo formado por: H-, HO-, halo-, NC-, HO-(C=O-, H2N-, (C1-C8)alquil-NH-, [(C1-C8)alquil]2N-, (C1-C8)alquil-opcionalmente sustituido con 1-3 átomos de flúor,(C1-C8) alquil-O- en donde el grupo alquilo es opcionalmente sustituido con 1-3 átomos de flúor, HO-(C1-C8)alquil-, (C1-C8)alquil-O-(C1-C8)alquil-, H2N-(C1-C8)alquil-, (C1-C8)alquilo NH-(C1-C8)alquil-, [(C1-C8)alquil]2N-(C1-

C8)alquil-, (C1-C8)alquil-(C=O)-, (C1-C8)alquil-(C=O)-(CC8) alquil-, (C6-C10)aril-, (C2-Cg) heteroaril-, (C6-C10) ariloxi, H2N-(C=O), H2N-(C=O)-(CC8) alquilo, (C1-C8)alquil-NH-(C=O)-, (C1-C8)alquil-NH-(C=O)-(C1-C8)alquil-, [(C1-C8)alquil]2N (C=O)-, [(C1-C8)alquil]2-N-(C=O)-(C1-C8)alquil-, (C3-C8)cicloalquil-, (C1-C8)alquil-SO2-, NC-(C C8)alquil-, (C1-C8) alquil-(C=O)-NH-, H2N-(C=O)-NH-, H2N-(C=O)-NH-(C1-C8) alquil-;

R5 es (C1-C8) alquil-.

para el tratamiento y prevención de la endometrosis.

Algunas realizaciones particularmente favorables de la presente invención son los siguientes compuestos según se informan en WO01/72728

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-me-til-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

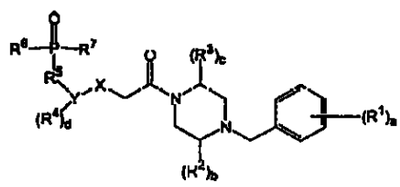
ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5- Bromo -2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- etansulfónico,

|La solicitud de patente WO2004/055031 en su totalidad se incorpora por referencia a la presente solicitud. Algunas

formas de realización ventajosas de acuerdo con la presente invención son los compuestos de la fórmula I- WO2004/055031



(I-WO2004/055031)

o una prodroga del mismo, o una sal aceptable para uso farmacéutico del compuesto o su prodroga; en donde

a = 0, 1, 2, 3, 4 o 5, b = 0, 1 o 2, c = 0, 1 o 2, d = 0, 1,2, 3 o 4;

X es O, S, CH2 o NR6,

Y es (C6-C10) arilo o (C2-C9) heteroarilo;

cada R1 es en forma independiente: hidroxi, halo,(C1-C8) alquilo opcionalmente sustituido con entre 1 y 3 átomos de flúor,(C1-C8) alcoxi opcionalmente sustituido con 1-3 átomos de flúor, HO(C1-C8) alquil-, ciano, amino, H2N (C1-C8) alquil-, carboxi, acilo, (C1-C8) alquil(C=O)(C1-C8)alquil-, H2N(C=O)-, o H2N (C=O)(C1-C8) alquil-;

cada R2 y R3 son en forma independiente: oxo,(C1-C8) alquilo opcionalmente sustituido con 1-3 átomos de flúor, (C3-C8) cicloalquil-, (C3-C8)cicloalquil-(C1-C8)alquil-, (C6-C10) aril-, (C6-C10) aril(C1-

C8)alquil-, HO(C1-C8) alquil-,(C1-C8) alquil-O-(C1-C8)alquil-, H2N(C1-C8) alquil-, (C1-C8)alquil-NH-(C1-C8)alquil-, [(C1-C8)alquil]2N-(C1-C8)alquil-, (C2-C9) heterociclil(C1-C8)alquil-, (C1-C8)alquil(C=O) NH(C1-C8) alquil-,(C1-C8)alquil-O-(C=O) NH (C1-C8) alquil-, H2N(C=O) NH(C1-C8) alquil-, (C1-C8)alquil-SO2-NH(C1-C8)alquil-, (C2- C9) heteroaril(C1-C8) alquil-, H2N (C=O), o H2N (C=O) (C1-C8)alquil-;

cada R4 es en forma independiente· HO-,halo-, NC-, HO(C=O)-, H2N-, (C1-C8)alquilo NH-, [(C1-C8)alquil] 2N-,(C1-C8) alquil-, opcionalmente sustituido con 1-3 átomos de flúor, (C1-C8) alcoxi opcionalmente sustituido con 1-3 átomos de flúor, HO (C1-C8) alquil-, (C1-C8) alquil-O-(C1-C8)alquil-, H2N(C1-C8)alquil--, (C1-C8)alquilNH(C1-C8)alquil-, [(C1-C8)alquil] 2N (C1- C8) alquil-, (C1-C8)alquil(C=O)-, (C1-C8)alquil(C=O)(C1-C8)alquil-, (C6-C10)aril-, (C2-Cg) heteroaril-, (C6-C10) ariloxi-, H2N(C=O)-, H2N (C=O)(C1-C8)alquil-, (C1-C8) alquilNH(C=O)-, (C1-C8)alquil-NH(C=O)(C1-C8)alquil-, [(C1-C8)alquil]2N(C=O)-, [(C1-C8) alquil] 2N (C=O) (C1-C8) alquil-, (C3-C8) cicloalquil-, (C1-C8)alquilSO2-, NC(C1-C8)-alquil(C=O)NH-, H2N(C=O)NH- o H2N(C=O)NH-(C1-C8)-alquil-;

R5 está unido a (C1-C8)-alquil-,

R6 es en forma independiente: hidroxi, amina o (C1-C8)-alquil-NH, y

R7 es en forma independiente: hidrógeno, hidroxilo, (C1-C8)-alquiloxi o (C1-C8)-alquil-

para el tratamiento y prevención de la endometrosis

Algunas realizaciones particularmente favorables de la presente invención son los siguientes compuestos según se informan en WO2004/055031

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfónico,

monoetiléster de ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R, 5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil) fosfónico,

ácido 5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfonamídico

En otro aspecto, esta invención provee composiciones farmacéuticas útiles para el tratamiento de la endometrosis en un humano de sexo femenino que necesita dicho tratamiento,y dicha composición comprende una cantidad eficaz en términos terapéuticos de un compuesto de fórmula (Ia) según se ha descrito,y un excipiente aceptable para uso farmacéutico.

En otro aspecto, esta invención provee un método para tratar y prevenir la endometrosis en un humano de sexo femenino, y dicho método comprende administrar a un humano de

sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de un compuesto de fórmula (Ia) según se ha descrito.

En otro aspecto, esta invención provee compuestos de fórmula (Ia) para la preparación de un medicamento para el tratamiento de la endometrosis

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Definiciones

Tal como se los utiliza en la memoria descriptiva y en las reivindicaciones adjuntas, salvo que se indique lo contrario, los siguientes términos tienen los significados que se indican:

"Alquilo" hace referencia a un radical monovalente o divalente de cadena lineal o ramificada que consiste exclusivamente de carbono e hidrógeno, sin insaturación alguna y con entre uno y ocho átomos de carbono, por ejemplo, metilo, etilo, *n*- propilo, 1-metiletilo (*iso*-propilo), *n*-butilo, *n*-pentilo, 1,1-dimetiletilo (*t*-butilo), *n* -heptilo, y similares.

"Alquilcarbonilo" hace referencia a un radical de la fórmula $-C(O)-R_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, acetilo, etilcarbonilo, *n*-propilcarbonilo, y similares.

"Alquilcarbonilalquilo" hace referencia a un radical de la fórmula $- R_a-C(O)-R_a$ donde cada R_a es en forma indepen-

diente un radical alquilo según se ha definido, por ejemplo, (acetil)metilo, 2-(acetil)etilo, 4- (ethylcarbonyl)butilo, y similares.

"Alquilcarbonilamino" hace referencia a un radical de la fórmula $-N(H)-C(O)-R_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, acetilamino, etilcarbonilamino, n-propilcarbonilamino, y similares

"(Alquilcarbonil)(alquil) amino" hace referencia a un radical de la fórmula $-N(R_a)-C(O)-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, *N*-metil-*N*- acetilamino, *N*-etil-*N*-(etilcarbonil)amino, y similares.

"Alquilcarbonilaminoalquilo" hace referencia a un radical de la fórmula $- R_a-N(H)C(O)-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, acetilammometilo, 2- (acetilamino)etilo, 4-(etilcarbonilamino)butilo, y similares.

"(Alquilcarbonil)(alquil)aminoalquilo" hace referencia a un radical de la fórmula $-R_a-N(R_a)-C(O)-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, (*N*-metil- *N*-acetilamino)metilo, 2-(*N*-etil-*N*-(etilcarbonil)amino) propilo, y similares.

"Alquiltio" hace referencia a un radical de la fórmula $-S-R_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, metiltio, etiltio, *n*- propiltio, y similares.

"Alquilsulfinilo" hace referencia a un radical de la fórmula $-S(O)R_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, metilsulfinilo, etilsulfinilo, *n*-propilsulfinilo, y similares.

"Alquilsulfonilo" hace referencia a un radical de la fórmula $-S(O)_2R_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, metilsulfonilo, etilsulfonilo, *n*-propilsulfonilo, y similares

"Alquiltioalquilo" hace referencia a un radical de la fórmula $-R_a-S-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., metiltiometilo, 2-metiltioetilo, 2-etiltiopropilo, y similares.

"Alquilsulfinilalquilo" hace referencia a un radical de la fórmula $-R_a-S(O)-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p. ej., metilsulfinilmetilo, 2-metilsulfiniletilo, 2- etilsulfinilpropilo, y similares

"Alquilsulfonilalquilo" hace referencia a un radical de la fórmula $-R_a-S(O)_2-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., metilsulfonilmetilo, 2-metilsulfoniletilo, 2-etilsulfonilpropilo, y similares.

"Alquilsulfonilamino" hace referencia a un radical de la fórmula $-N(H)-S(O)_2-R_a$ donde R_a es un radical alquilo según se ha definido, p.ej., metilsulfonilamino, etil-

sulfonilamino, *iso*-propilsulfonilamino, y similares.

"Alquilsulfonilaminoalquilo" hace referencia a un radical de la fórmula $-R_a-N(H)-S(O)_2-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., metilsulfonilaminometilo, 2-(etilsulfonilamino) etilo, 3-(*iso*-propilsulfonilamino)propilo, y similares.

"(Alquilsulfonil)(alquil)aminoalquilo" hace referencia a un radical de la fórmula $-R_a-N(R_a)-S(O)_2-R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., (metilsulfonil)(metil)aminometilo, 2-((etilsulfonil)(metil)amino) etilo, 3-((*iso*-propilsulfonil)(etil)amino)propilo, y similares.

"Alquenilo" hace referencia a un radical monovalente o divalente de cadena lineal o ramificada que consiste exclusivamente de carbono e hidrógeno, que contiene al menos una doble ligadura y con entre dos y ocho átomos de carbono, p.ej., etenilo, prop-1-enilo, but-1-enilo,pent-1-enilo,penta-1,4-dienilo, y similares.

"Alquenilcarbonilamino" hace referencia a un radical de la fórmula $-N(H)-C(O)-R_c$ donde R_c es un radical alquenilo según se ha definido,p.ej., etenilcarbonilamino, prop-2-enilcarbonilamino,but-2-enilcarbonilamino, y similares.

"Alquinilo" hace referencia a un radical monovalente o divalente de cadena lineal o ramificada que consiste exclusivamente de carbono e hidrógeno, que contiene al menos

una ligadura triple y con entre dos y ocho átomos de carbono, p ej., etinilo, prop-1-inilo, but-1-inilo, pent-1-inilo, pent-3-inilo, y similares.

"Alcoxi" hace referencia a un radical de la fórmula $-OR_a$ donde R_a es un radical alquilo según se ha definido. por ejemplo, metoxi, etoxi, *n*-propoxi, 1-metiletoxi (*iso*-propoxi), *n*-butoxi, *n*-pentoxi 1,1- dimetiletoxi (*t*-butoxi), y similares.

"Alcoxicarbonilo" hace referencia a un radical de la fórmula $-C(O)OR_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, metoxicarbonilo, etoxicarbonilo, *n*-propoxicarbonilo, y similares.

"Alcoxicarbonilalquilo" hace referencia a un radical de la fórmula $-R_a-C(O)OR_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p. ej., metoxicarbonilmetilo, 2-(etoxicarbonil)etilo, 2- (metoxicarbonil)propilo, y similares.

"Alcoxialquilcarboniloxialquilo" hace referencia a un radical de la fórmula $-R_a-OC(O)-R_a-OR_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, metoximetilcarboniloximetilo, 2-(2-(2- (etoxi)etilcarboniloxi)etil) etilo, 2-(3-(2-(etoxi)etilcarboniloxi) propil)etilo, y similares

"Alcoxicarbonilamino" hace referencia a un radical de la fórmula $-N(H)-C(O)-OR_a$ donde R_a es un radical alquilo

según se ha definido, p.ej , metoxicarbonilamino, etoxicarbonilamino, isopropoxicarbonilamino, y similares.

"(Alcoxicarbonil)(alquil)amino" hace referencia a un radical de la fórmula $-N(R_a)(C(O)OR_a)$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, *N*-metil-*N*- metoxicarbonilamino, *N*-etil-*N*-etoxicarbonilamino, y similares.

"Alcoxicarbonilaminoalquilo" hace referencia a un radical de la fórmula $- R_a-N(H)-C(O)-OR_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., metoxicarbonilaminometilo, 2-(etoxicarbonilamino) etilo, isopropoxicarbonilaminometilo, y similares

"(Alcoxicarbonil)(alquil)aminoalquilo" hace referencia a un radical de la fórmula $- R_a-N(R_a)(C(O)OR_a)$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., *N*-metil-*N*-metoxicarbonilaminometilo, 2-(*N*-etil- *N*-etoxicarbonilamino)etilo, y similares.

"(Alcoxi)aralquilo" hace referencia a un radical aralquilo en donde el grupo alquilo en el mismo es sustituido por un radical alcoxi según se ha definido, por ejemplo, 2-fenil- 1-metoxietilo, fenil(metoxi)metilo, y similares.

"Alcoxialquilcarbonilamino" hace referencia a un radical de la fórmula $-N(H)-C(O)- R_a-O-R_a$ donde cada R_a es un radical alquilo según se ha definido, por ejemplo, metoximetilcarbonilamino, etoxietilcarbonilamino, metoxietilcar-

bonilamino, y similares.

"Alcoxicarbonilalquilcarbonilamino" hace referencia a un radical de la fórmula - N(H)-C(O)-R_a-C(O)OR_a donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej. etoxicarbonilmetilcarbonilamino, metoxicarbonilmetilcarbonilamino, (2-etoxicarboniletil)car-bonilamino, (2-metoxicarboniletil)carbonilamino, y similares.

"Alcoxicarbonilalquilcarbonilaminoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)-C(O)-R_a-C(O) OR_a donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., etoxicarbonilmetilcarbonilaminometilo, 2-(metoxicarbonilmetilcarbonilamino)etilo, 1-((2-etoxicarboniletil) carbonilamino)etilo, (2-metoxicarboniletil)carbonilaminometilo, y similares.

"(Alcoxicarbonilalquil)aminocarbonilo" hace referencia a un radical de la fórmula -C(O)-N(H)-R_a-C(O)-OR_a donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, (metoxicarbonilmetil) aminocarbonilo, (2-(etoxicarbonil)etil)aminocarbonilo, (1-(metoxicarbonil)etil)aminocarbonilo, y similares.

"(Alcoxicarbonilalquil)ureidoalquilo" hace referencia a un radical de la fórmula - R_a-N(H)-C(O)-N(H)-R_a-C(O)-OR_a donde cada R_a es en forma independiente un radical alquilo según se ha definido y donde el nitrógeno al cual

$-R_a-$ C(O)-OR_a está unido se indica como "*N*"', p.ej , (etoxicarbonilmetil)ureidometilo, (2-(etoxicarbonil)etil)ureidometilo, 2-((2-(etoxicarbonilmetil) ureidometilo, y similares

"(Alcoxicarbonilalquilcarbonil)(alquil)glicinamido" hace referencia a un radical de la fórmula -N(H)-C(O)-CH_2-N(R_a)-C(O)-R_a- C(O)-OR_a donde cada R_a es en forma independiente un radical alquilo según se ha definido, p ej., (metoxicarbonilmetilcarbonil)(metil) glicinamido,((2-etoxicarboniletil)carbonil)(etil)glicinamido,y similares.

"(Alcoxialquilcarbonil)glicinamido" hace referencia a un radical de la fórmula -N(H)-C(O)-CH_2-N(H)-C(O)-R_a-O-R_a donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., (metoxiacetil)glicinamido, (etoxiacetil)glicinamido, y similares.

"Cadena alquileno" se refiere un radical divalente de cadena lineal o ramificada que consiste exclusivamente de carbonilo y hidrógeno, sin insaturación alguna y con entre uno y ocho átomos de carbono, p.ej., metileno, etileno, propileno, *n*-butileno, y similares.

"Cadena alquilideno" hace referencia a un radical divalente insaturado de cadena lineal o ramificada que consiste exclusivamente de átomos de carbono e hidrógeno, con entre uno y ocho átomos de carbono, en donde la insatura-

ción está presente solamente en forma de enlaces dobles y en donde puede existir un enlace doble entre el primer carbono de la cadena y el resto de la molécula, por ej., etilideno, propilideno, *n*-butilideno, y similares

"Amino" se refiere al radical $-NH_2$.

"Aminoalquilo" hace referencia a un radical de la fórmula $-R_aNH_2$ donde R_a es un radical alquilo según se ha definido, por ejemplo, aminometilo, 2-aminoetilo, 3-aminopropilo, 2-aminopropilo, y similares.

"Aminoalquilamino" hace referencia a un radical de la fórmula $-N(H)-R_a-NH_2$ donde R_a es un radical alquilo según se ha definido, p ej., aminometilamino, (2-aminoetil)amino, (2-aminopropil)amino, y similares.

"Aminoalcoxi" hace referencia a un radical de la fórmula $-OR_a-NH_2$ donde R_a es un radical alquilo según se ha definido, p.ej., aminometoxi, 2- aminoetoxi, 3-aminopropoxi, 2-aminopropoxi, 4-aminobutoxi, y similares

"Aminocarbonilo" se refiere al radical $-C(O)NH_2$.

"Aminocarbonilglicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(H)-C(O)-NH_2$.

"(Aminocarbonil)(alquil)glicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(R_a)-C(O)-NH_2$ donde R_a es un radical alquilo según se ha definido y donde el nitrógeno con el sustituyente R_a se designa como "*N*",p.ej., (aminocarbonil)(*N'*-metil)glicinamido, (amino-

carbonil)(*N'*- etil)glicinamido, y similares.

"Aminocarbonilalquilo" hace referencia a un radical de la fórmula - R_a-C(O)NH_2 donde R_a es un radical alquilo según se ha definido, p ej., aminocarbonilmetilo, 2-(aminocarbonil)etilo, 2-(aminocarbonil)propilo, y similares.

"(Aminocarbonilalquil)aminocarbonilo" hace referencia a un radical de la fórmula - C(O)-N(H)-R_a-C(O)-NH_2 donde R_a es un radical alquilo según se ha definido, p ej., (aminocarbonilmetil)aminocarbonilo, (2-aminocarboniletil)aminocarbonilo, (1-aminocarboniletil)aminocarbonilo, y similares.

"(Aminoalquil) aminocarbonilo" hace referencia a un radical de la fórmula -C(O)-N(H)-R_a -NH_2 donde R_a es un radical alquilo según se ha definido, p.ej., (aminometil) aminocarbonilo, (2-aminoetil)aminocarbonilo, (1-aminoetil)aminocarbonilo, y similares.

"Amidino" se refiere al radical -C(NH)NH_2.

"Arilo" hace referencia a un radical fenilo o naftilo Salvo que se indique expresamente lo contrario en la memoria descriptiva, el término "arilo" o el prefijo "ar-" (por ejemplo en "aralquilo") pretenden incluir radicales arilo sustituidos opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, mercapto, halo, alquilo, alquenilo, alquinilo, fenilo, fenilalquilo, fenilalquenilo, alcoxi, fenoxi, fenilalcoxi,

haloalquilo, haloalcoxi, formilo, nitro, ciano, amidino, cicloalquilo, hidroxialquilo, alcoxialquilo, fenoxialquilo, fenilalcoxialquilo, amino, monoalquilamino, dialquilamino, monofenilamino, monofenilalquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monofenilaminoalquilo, monofenilalquilaminoalquilo, alquilcarbonilo, carboxi, alcoxicarbonilo, carpoxialquilo, alcoxicarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, según se define en la presente.

"Arilcarbonilo" hace referencia a un radical de la fórmula -$C(O)R_b$ donde R_b es un radical arilo según se ha definido, por ejemplo, fenilcarbonilo y naftalen-2-ilcarbonilo, y similares

"Arilcarbonilalquilo" hace referencia a un radical de la fórmula -$R_aC(O)R_b$ donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, p.ej., fenilcarbonilmetilo, 2-(fenilcarbonil)etilo, 3-(naftalen-2-ilcarbonil) propilo, y similares

"Arilcarbonilaminoalquilo" hace referencia a un radical de la fórmula - R_a-N(H)-C(O)-R_b donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, p.ej., (4-metoxifenil)carbonilaminometilo, 2-((4-fluorofenil)carbonilamino) etilo, 1-((4-

clorofenil)carbonilamino)etilo, y similares.

"Arilsuffonilo" hace referencia a un radical de la fórmula -$S(O)_2$-R_b donde R_b es un radical arilo según se ha definido, por ejemplo, fenilsulfonilo, (4- clorofenil)sulfonilo, (3-nitrofenil)sulfonilo, y similares.

"Arilsulfonilamino" hace referencia a un radical de la fórmula -N(H)-$S(O)_2$-R_b donde R_b es un radical arilo según se ha definido, por ejemplo, fenilsulfonilamino, (4-clorofenil)sulfonilamino, (4-fluorofenil)sulfonilamino, (3-nitrofenil) sulfonilamino, y similares.

"Arilsulfonilaminoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)-$S(O)_2$-R_b donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, por ejemplo, fenilsulfonilaminometilo, (4-clorofenil) sulfonilaminometilo, 2-((4-fluorofenil)sulfonilamino)etilo, 1-((3- nitropnenil)sulfonilamino)etilo, y similares.

"(Arilsulfonil) (alquil)aminoalquilo" hace referencia a un radical de la fórmula -R_a-N(R_a)-$S(O)_2$-R_b donde cada R_a es en forma independiente un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, por ejemplo, (fenilsulfonil)(metil) aminometilo, ((4-clorofenil)sulfonil)(etil)aminometilo, 2-(((4-fluorofenil)sulfonil)(metil)amino)etilo, 1-(((3-nitrofenil)sulfonil) (etil)amino)etilo, y similares.

"(Alcoxicarbonilaminoalquilcarbonil)glicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(H)-C(O)-N(H)-C(O)-OR_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, (etoxicarbonilaminocarbonil)glicinamido, (metoxicarbonilaminocarbonil)glicinamido, y similares

"Arilcarbonilglicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(H)-C(O)-R_b$ donde R_b es un radical arilo según se ha definido, por ejemplo, fenilcarbonilglicinamido, (4-fluoro-3-trifluorometilfenil) carbonilglicinamido, (4-fluorofenil)carbonilglicinamido, y similares.

"(Arilcarbonil)(alquil)glicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(R_a)-C(O)-R_b$ donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido y el nitrógeno al cual el R_a radical está unido se designa como "*N*"', por ejemplo, (fenilcarbonil)(*N'*-metil) glicinamido, ((4-fluoro-3-trifluorometilfenil)carbonil) (*N'*-etil)glicinamido, ((4-fluorofenil)carbonil)(*N'*-metil) glicinamido, y similares.

"Aralquilo" hace referencia a un radical de la fórmula $-R_aR_b$ donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, por ejemplo, bencilo, y similares

"Aralquilcarbonilo" hace referencia a un radical de la fórmula $-C(O)-R_d$ donde R_d es un radical aralquilo según se ha definido, por ejemplo, bencilcarbonilo, 1-(fenil)etilcarbonilo, y similares

"Aralquilcarbonilalquilo" hace referencia a un radical de la fórmula $-R_aC(O)R_d$ donde R_a es un radical alquilo según se ha definido y R_d es un radical aralquilo según se ha definido, por ejemplo, bencilcarbonilmetilo, 2-(1-(fenil)etilcarbonil)etilo, y similares

"Aralquenilo" hace referencia a un radical de la fórmula $-R_cR_b$ donde R_b es un radical arilo según se ha definido y R_c es un radical alquenilo según se ha definido, por ejemplo, 3-fenilpropilid-1-enilo, y similares.

"Ariloxi" hace referencia a un radical de la fórmula $-OR_b$ donde R_b es un radical arilo según se ha definido, por ejemplo, fenoxi y naftoxi, y similares

"Aralcoxicarbonilo" hace referencia a un radical de la fórmula $-C(O)OR_d$ donde R_d es un radical aralquilo según se ha definido, p ej., benciloxicarbonilo, y similares

"Aralcoxicarbonilalquilo" hace referencia a un radical de la fórmula $-R_a C(O)OR_d$ donde R_a es un radical alquilo según se ha definido y R_a es un radical aralquilo según se ha definido, por ejemplo, benciloxicarbonilmetilo, 2- (benciloxicarbonil)etilo, 3-((naftalen-2-il)oxi)carbonil)propilo, y similares.

"Ariloxialquilo" hace referencia a un radical de la fórmula - R_a-OR_b donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido. por ejemplo, fenoximetilo, 2-(fenoxi) etilo, 3-(fenoxi)propilo, y similares.

"Ariloxialquilcarboniloxialquilo" hace referencia a un radical de la fórmula -R_a-OC(O)-R_a- OR_b donde cada R_a es en forma independiente un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, p ej.,fenoximetilcarboniloximetilo, (2- fenoxietil)carboniloximetilo, 3-((2-fenoxietil)carboniloxi)propilo, y similares.

"Aralcoxi" hace referencia a un radical de la fórmula - OR_d donde R_d es un radical aralquilo según se ha definido, por ejemplo, benciloxi, y similares.

"Aralcoxilalquilo" hace referencia a un radical de la fórmula -R_a-OR_d donde R_a es un radical alquilo según se ha definido y R_d es un radical aralquilo según se ha definido, por ejemplo, benciloximetilo, 2- feniletoximetilo, y similares

"Aralcoxialquilcarboniloxialquilo" hace referencia a un radical de la fórmula -R_a-OC(O)-R_a-OR_d donde cada R_a es en forma independiente un radical alquilo según se ha definido y R_d es un radical aralquilo según se ha definido, por ejemplo, benciloximetilcarboniloximetilo, (2-(fenil)

etoximetil)carboniloximetilo, 2-((2-(fenil)etoximetil)carboniloxi) etilo, y similares.

"Alcoxialquilo" hace referencia a un radical de la fórmula -R_a OR_a donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, metoxietilo, etoximetilo, propoximetilo, propoxietilo, y similares

"Alaninamido" hace referencia a un radical de la fórmula -N(H)- C(O)-C(CH_3)H-NH_2.

"Alanimamidoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)-C(O)-C(CH_3)H-NH_2 donde R_a es un radical alquilo según se ha definido, por ejemplo , alaninamidometilo, 2-(alaninamido)etilo, 1-(alaninamido)etilo, 3- (alaninamido)propilo, y similares.

"Azidoalquilo" se refiere un radical de la fórmula -R_a-N_3 donde R_a es un radical alquilo según se ha definido, por ejemplo, 2-azidoetilo, 3-azidopropilo, 2-azidopropilo, 4-azidobutilo, y similares

"Bencilo" hace referencia a un radical de la fórmula -CH_2-R_h donde R_h es un radical fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, alquilo, haloalquilo, alcoxi, alquenilo, nitro, ciano, amino, monoalquilamino, dialquilamino, alquilcarbonilo, carboxi, alcoxicarbonilo, y aminocarbonilo.

"Bencilcarbonilo" hace referencia a un radical de la fórmula

$-C(O)-CH_2-R_h$ donde R_h es un radical fenilo según se ha definido, por ejemplo, (4-metoxibencil)carbonilo, (3-fluorobencil)carbonilo, y similares

"Carboxi" se refiere al radical -C(O)OH.

"Carboxialquilo" se refiere al radical de la fórmula $-R_a-C(O)OH$ donde R_a es un radical alquilo según se ha definido, por ejemplo, carboximetilo, 2- carboxietilo, 3-carboxipropilo, y similares.

"(Carboxialquil) aminocarbonilo" hace referencia a un radical de la fórmula $-C(O)-N(H)-R_a-C(O)OH$ donde R_a es un radical alquilo según se ha definido, por ejemplo, (carboximetil)aminocarbonilo, (2-carboxietil)aminocarbonilo, (1-carboxietil)aminocarbonilo, y similares.

"Sistema de anillo carbocíclico" hace referencia a un radical estable de 3 a 15 miembros que consiste exclusivamente de átomos de carbono e hidrógeno. A los efectos de esta invención, el radical de sistema de anillo carbocíclico puede ser un sistema de anillo monocíclico, bicíclico o tricíclico, y puede incluir sistemas de anillo fusionados o en forma de puente, y el sistema de anillo puede ser parcial o totalmente saturado o aromático, y los átomos de carbono en el sistema de anillo puede ser opcionalmente oxidado Ejemplos de tales radicales de sistema de anillo carbocíclico incluyen, sin carácter taxativo, ciclopropilo, ciclobutilo, ciclohexilo, nor-

bornano, norborneno, adamantilo, biciclo[2.2.2]octano, fenilo, naftilo, indenilo, azulenilo, fluorenilo, anthracenilo, y similares.

"Cicloalquilo" hace referencia a un radical monocíclico o bicíclico estable de 3 a 10 miembros que es saturado, y que consiste exclusivamente de átomos de carbono e hidrógeno, por ejemplo, ciclopropilo, ciclobutilo, ciclobutilo, ciclohexilo, decalinilo y similares Salvo que si indique específicamente lo contrario en la memoria descriptiva, el término "cicloalquilo" pretenden incluir radicales cicloalquilo que se sustituyen opcionalmente por uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por alquilo, halo, hidroxi, amino, nitro, alcoxi, carboxi, fenilo y alcoxicarbonilo.

"Cicloalquilalquilo" hace referencia a un radical de la fórmula $-R_a-R_e$ donde R_a es un radical alquilo según se ha definido y R_e es un radical cicloalquilo según se ha definido, por ejemplo, ciclopropilmetilo, 2- ciclobutiletilo, 3-ciclohexilpropilo, y similares.

"Cicloalquilamino" hace referencia a un radical de la fórmula $-N(H)-R_e$ donde R_e es un radical cicloalquilo según se ha definido, por ejemplo, ciclopropilamino, ciclobutilamino, ciclohexilamino, y similares.

"Cicloalquilaminoalquilo" hace referencia a un radical de la

fórmula $-R_a-N(H)-R_e$ donde R_a es un radical alquilo según se ha definido y R_e es un radical cicloalquilo según se ha definido, p.ej., ciclopropilaminometilo, 2-(ciclobutilamino)etilo, ciclohexilaminometilo, y similares

"(Cicloalquilalquil)amino" hace referencia a un radical de la fórmula $-N(H)-R_a-R_e$ donde R_a es un radical alquilo según se ha definido y R_e es un radical cicloalquilo según se ha definido, p.ej., (ciclopropilmetil)amino, (2-ciclobutiletil) amino, (3-ciclohexilpropil)amino, y similares.

"(Cicloalquilalquil)aminoalquilo" hace referencia a un radical de la fórmula $-R_a-N(H)-R_a-R_e$ donde cada R_a es en forma independiente un radical alquilo según se ha definido y R_e es un radical cicloalquilo según se ha definido, p. ej., (ciclopropilmetil)aminometilo, 2-((2-ciclobutiletil)amino)etilo, (3-ciclohexilpropil)aminometilo, y similares.

"Cicloalquilcarbonilamino" hace referencia a un radical de la fórmula $-C(O)-N(H)-R_e$ donde R_e es un radical cicloalquilo según se ha definido, por ejemplo, ciclopropilcarbonilamino, (2-fenilciclopropil)carbonilamino, ciclohexilcarbonilamino, 4-cianodecalinilcarbonilamino. ciclopentilcarbonilamino, y similares

"Cicloalquilcarbonilaminoalquilo" hace referencia a un radical de la fórmula $-R_a-C(O)-N(H)-R_e$ donde R_a es un radi-

cal alquilo según se ha definido y R_e es un radical cicloalquilo según se ha definido, por ejemplo, ciclopropilcarbonilaminometilo, 2-((2- fenilciclopropil) carbonilamino)etilo, 1-(ciclohexilcarboniamino)etilo, (3- fenilciclopentil)carbonilaminometilo, y similares.

"Cicloalquilalquilcarbonilamino" hace referencia a un radical de la fórmula -C(O)- N(H)-R_a-R_e donde R_a es un radical alquilo según se ha definido y R_e es un radical cicloalquilo según se ha definido, por ejemplo, (ciclopropilmetil) carbonilamino, ((2-fenilciclopropil)metil)carbonilamino, (2- ciclohexiletil)carbonilamino, (1-ciclohexiletil)carbonilamino, y similares.

"Ciano" se refiere al radical -CN.

"Cianoalquilo" hace referencia a un radical de la fórmula -R_aCN donde R_a es un radical alquilo según se ha definido, cianometilo, 2- (ciano)etilo, 3-(ciano)propilo, y similares.

"DMF" hace referencia a N,N- dimetilformamida.

"DMSO" hace referencia a dimetilsulfóxido.

"Dialquilamino" hace referencia a un radical de la fórmula -N(R_a)R_a donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, dimetilamino, metiletilamino, dietilamino, dipropilamino, etilpropilamino, y similares.

"Dialquilaminoalquilo" hace referencia a un radical de la

fórmula $-R_a-N(R_a)\ R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p. ej., dimetilaminometilo, metiletilaminometilo, 2-dietilaminoetilo, 3-dipropilaminopropilo, y similares.

"Dialquilaminocarbonilo" hace referencia a un radical de la fórmula $-C(O)N(R_a)R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, por ejemplo, dimetilaminocarbonilo, metiletilaminocarbonilo, dietilaminocarbonilo, dipropilaminocarbonilo, etilpropilaminocarbonilo, y similares.

"Dialquilaminocarbonilalquilo" hace referencia a un radical de la fórmula $-R_a-C(O)N(R_a)R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej , dimetilaminocarbonilmetilo, 2-(metiletilaminocarbonil)etilo, 3-(dietilaminocarbonil)propilo, 2- (dipropilaminocarbonil)propilo, y similares

"Dialquilaminocarboniloxialquilo" hace referencia a un radical de la fórmula $-R_a-O-C(O)-N(R_a)R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido,p.ej , dimetilaminocarboniloximetilo, 2- (metiletilaminocarboniloxi)etilo, 3-(dietilaminocarboniloxi)propilo, 2- (dipropilaminocarboniloxi)propilo, y similares

"Dialquilureido" hace referencia a un radical de la fórmula $-N(H)-C(O)-N(R_a)(R_a)$ o un radical de la fórmula $-N(R_a)-C(O)-N(R_a)H$ donde cada R_a es en forma independiente un

radical alquilo según se ha definido y y el nitrógeno de unión se designa como "N" y el otro nitrógeno se designa como "N", por ejemplo, *N'*,*N'*-di(metil) ureido, *N'*-metil-*N'*-etilureido, *N'*,*N'*-di(etil) ureido, *N'*,*N'*-di(propil)ureido, *N*-metil-*N'*- etilureido, y similares.

"Diarilureido" hace referencia a un radical de la fórmula -N(H)-C(O)-N(R_b)(R_b) o un radical de la fórmula -N(R_b)-C(O)-N(R_b)H donde cada R_b es en forma independiente un radical arilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*", por ejemplo, *N'*,*N'*-di(fenil)ureido, *N'*-fenil-*N'*-(3-nitro) fenilureido, *N'*,*N'*-di(4-metoxifenil)ureido, *N'*,*N'*-di(4- clorofenil) ureido, *N*-4-clorofenil-*N'*-(3-clorofenil) ureido y similares

"Dialquilureidoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)-C(O)-N(R_a) (R_a) o un radical de la fórmula -R_a-N(R_a)-C(O)-N(R_a)H donde cada R_a es en forma independiente un radical alquilo según se ha definido y el nitrógeno unido se designa como "*N*" y el otro nitrógeno se designa como "*N*"', por ejemplo, *N'*,*N'*- di(metil) ureidometilo, 2-(*N'*-metil-*N'*-etilureido)etilo, 1-(*N'*,*N'*-di(etil)ureido)etilo, 3-(*N'*,*N'*- di(propil)ureido propilo, 2-(*N*-metil-*N'*-etilureido)etilo, y similares.

"Formilo" se refiere al radical -C(O)H.

"Formilalquilo" hace referencia a un radical -R_a-C(O)H donde

R_a es un radical alquilo según se ha definido, por ejemplo, formilmetilo, 2-(formil)etilo, 3-(formil)propilo, y similares

"Glicinamido" hace referencia a un radical de la fórmula -N(H)-C(O)-CH_2 -NH_2.

"Glicinamidoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)-C(O)- CH_2- NH_2 donde R_a es un radical alquilo según se ha definido, por ejemplo, glicinamidometilo. 2-(glicinamido)etilo, 1-(glicinamido)etilo, 3-(glicinamido)propilo, y similares.

"Guanidino" se refiere al radical -N(H)-C(NH)-NH_2.

"Halo" hace referencia a bromo, cloro, iodo o fluoro

"Haloalquilo" hace referencia a un radical alquilo, según se ha definido, que se sustituye con uno o más radicales halo, según se ha definido, por ejemplo, trifluorometilo, difluorometilo, triclorometilo, 2-trifluoroetilo, 1-fluorometil-2-fluoroetilo, 3-bromo- 2-fluoropropilo, 1-bromometil-2-bromoetilo, y similares.

"Haloalcoxi" hace referencia a un radical de la fórmula -OR_f donde R_f es un radical haloalquilo según se ha definido, por ejemplo, trifluorometoxi, difluorometoxi, triclorometoxi, 2,2,2-trifluoroetoxi, 1-fluorometil-2-fluoroetoxi, 3- bromo-2-fluoropropoxi, 1-bromometil-2-bromoetoxi, y similares.

"Haloalquilcarbonilamino" hace referencia a un radical de la

fórmula -N(H)-C(O) -R_f donde R_f es un radical haloalquilo según se ha definido, por ejemplo, trifluorometilcarbonilamino, trifluorometilcarbonilamino, 2-bromoetilcarbonilamino, y similares

"(Haloalquilcarbonil)ureido" hace referencia a un radical de la fórmula - N(H)-C(O)-N(H)-C(O)-R_f donde R_f es un radical haloalquilo según se ha definido, p.ej., (tricloro-metilcarbonil)ureido, (3-fluoropropilcarbonil)ureido, y similares.

"(Haloalquil)(alquil)ureidoalquilo" hace referencia a un radical de la fórmula -R_a-N(R_a)-C(O)-N(H)-R_f o a un radical de la fórmula -R_a- N(R_f)-C(O)-N(H)-R_a o un radical de la fórmula -R_a-N(H)-C(O)-N(R_a) R_f donde cada R_a es en forma independiente un radical alquilo según se ha definido y R_f es un radical haloalquilo según se ha definido y el nitrógeno terminal se designa como "*N*"' y el otro nitrógeno se designa como "*N*", por ej-, *N'*-(2-cloroetil)-*N*-(metil)ureidometilo, y 2-(*N'*-(2- cloroetil)-*N*-(metil)ureido)etilo, y similares.

"Haloalquilcarbonilaminoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)-C(O)-R_f donde R_a es un radical alquilo según se ha definido y R_f es un radical haloalquilo según se ha definido, por ejemplo, trifluorometilcarbonilaminometilo, 2-(trifluorometilcarbonilamino)etilo, y similares.

"Hidroxi" se refiere al radical -OH.

"Hidroxialquilo" hace referencia a un radical alquilo según se ha definido que está sustituido con un radical hidroxi, por ejemplo, hidroximetilo, 2- hidroxietilo, 2-hidroxipropilo, 3-hidroxipropilo, 4-hidroxibutilo, 3-hidroxibutilo, y similares

"(Hidroxialquil)aminocarbonilo" hace referencia a un radical de la fórmula $-C(O)-N(H)-R_a-OH$ donde R_a es un radical alquilo según se ha definido, por ejemplo, hidroximetilaminocarbonilo, (2-hidroxietil)aminocarbonilo, (1-hidroxietil)aminocarbonilo, y similares.

"Hidroxialcoxi" hace referencia a un radical de la fórmula $-OR_a-OH$ donde R_a es un radical alquilo según se ha definido, por ejemplo, 2- hidroxietoxi, 2-hidroxipropoxi, 4-hidroxibutoxi, 3-hidroxibutoxi, y similares.

"(Hidroxialcoxi)carbonilo" hace referencia a un radical de la fórmula $-C(O)-OR_a-OH$ donde R_a es un radical alquilo según se ha definido, por ejemplo, (2-hidroxietoxi)carbonilo, (2-hidroxipropoxi)carbonilo, (4-hidroxibutoxi)carbonilo, (3-hidroxibutoxi) carbonilo, y similares

"(Hidroxi)aralquilo" hace referencia a un radical aralquilo según se ha definido en donde el radical alquilo en el mismo es sustituido por un radical hidroxi, por ejemplo, (fenil)(hidroxi)metilo, 2-fenil-1- hidroxietilo, 2-fenil-3-hidroxipropilo, y similares

"(Hidroxialquiltio) alquilo" hace referencia a un radical alquiltioalquilo según se ha definido que está sustituido con un radical hidroxi, por ejemplo, 2- hidroxetiltiometilo, 2-(hidroximetiltio)etilo, y similares

"Hidroxialquenilo" hace referencia a un radical alquenilo según se ha definido que está sustituido con un radical hidroxi, por ejemplo, 3-hidroxiprop-1-enilo, 4- hidroxibut-1-enilo, 4-hidroxipent-1- enilo, 5-hidroxipenta-1,3-dienilo, y similares.

"Hidroxialquinilo" hace referencia a un radical alquinilo según se ha definido que está sustituido con un radical hidroxi, por ejemplo, 3- hidroxiprop-inilo, 4-hidroxipent-2-inilo, 1-hidroxibut-3-inilo, y similares.

"(Hidroxi)cicloalquilalquilo" hace referencia a un radical de la fórmula - $R_a(OH)-R_e$ donde R_a es un radical alquilo según se ha definido y R_e es un radical cicloalquilo según se ha definido y donde el radical OH es un sustituyente sobre cualquier carbono del radical Ra, p ej ,2-ciclopropil-1-hidroxietilo, (4-hidroxiciclohexil)metilo, y similares.

"Hidroxialquilaminoalquilo" hace referencia a un radical monoalquilaminoalquilo según se define más adelante que está sustituido con un radical hidroxi, p.ej , 2-hidroxietilaminometilo, 2-(3-hidroxipropilamino)etilo, y similares.

"Hidroxiamidino" hace referencia a un radical de la fórmula $-C(NH_2)=NOH$.

"Sistema de anillo heterocíclico" hace referencia a un radical estable de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre. A los efectos de esta invención, el radical de sistema de anillo heterocíclico puede ser un sistema de anillo monocíclico, bicíclico o tricíclico, que puede incluir sistemas de anillo fusionados o en forma de puente; y los átomos de nitrógeno, carbono o azufre en el radical de sistema de anillo heterocíclico pueden estar opcionalmente oxidados, el átomo de nitrógeno puede estar opcionalmente cuaternizado, y el sistema de anillo heterocíclico puede ser parcial o totalmente saturado o aromático. el sistema de anillo heterocíclico puede estar unido a la estructura principal en cualquier heteroátomo o átomo de carbono que resulta en la creación de un compuesto estable Ejemplos de tales radicales heterocíclicos incluyen, sin carácter taxativo, azepinilo, acridinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, benzopiranilo, benzopiranonilo, benzofuranilo, benzofuranonilo, benzotienilo, carbazolilo, cinnolinilo, decahidroisoquinolilo, dioxolanilo, furanilo, isotiazolilo, quinuclidinilo, imidazolilo, imidazolinilo, imidazo-

lidinilo, isotiazolidinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, indanilo, indolizinilo, isoxazolilo, isoxazolidinilo, morfolinilo, naftiridinilo, oxadiazolilo, octahidroindolilo, octahidroisoindolilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2- oxopirrolidinilo, 2-oxoazepinilo, oxazolilo, oxazolidinilo, piperidinilo, piperazinilo, 4- piperidonilo, fenazinilo, fenotiazinilo, fenoxazinilo, ftalazinilo, pteridinilo, purinilo, pirrolilo, pirrolidinilo, pirazolilo, pirazolidinilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, quinazolinilo, quinoxalinilo, quinolinilo, quinuclidinilo, isoquinolinilo, tiazolilo, tiazolidinilo, tiadiazolilo, triazolilo, tetrazolilo, tetrahidrofurilo, triazinilo, tetrahidropiranilo, tienilo, tiamorfolinilo, tiamorfolinilo sulfóxido, y tiamorfolinilsulfona.

"Heterociclilo" hace referencia a un sistema de anillo heterocíclico según se ha definido. Salvo que se indique expresamente lo contrario en la memoria descriptiva, el término "heterociclilo" pretenden incluir un sistema de anillo heterocíclico según se ha definido que es que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, mercapto, halo, alquilo, alquenilo, alquinilo, fenilo, fenilalquilo, fenilalquenilo, alcoxi, fenoxi, fenilalcoxi, haloalquilo, haloalcoxi, formilo, nitro, ciano, amidino,

cicloalquilo, hidroxialquilo, alcoxialquilo, fenoxialquilo, fenilalcoxialquilo, amino, monoalquilamino, dialquilamino, monofenilamino, monofenilalquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monofenilaminoalquilo, monofenilalquilaminoalquilo, carboxi, alcoxicarbonilo, fenilcarbonilo, bencilcarbonilo, alquilcarbonilo, carboxialquilo, alcoxicarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, fenilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, ureido, monoalquilureido, monofenilureido, monobencilureido, según se define en la presente.

"Heterociclilalquilo" hace referencia a un radical de la fórmula $-R_aR_g$ donde R_a es un radical alquilo según se ha definido y R_g es un radical heterociclilo según se ha definido,p.ej ,indolinilmetilo o imidazolilmetilo, y similares.

"Heterociclilamino" hace referencia a un radical de la fórmula - N(H)- R_g donde R_g es un radical heterociclilo según se ha definido, por ejemplo, oxazol-2-ilamino; piperidin-4- ilamino, y similares

"Heterociclilaminoalquilo" hace referencia a un radical de la fórmula $-R_a-N(H)-R_g$ donde R_a es un radical alquilo según se ha definido y R_g es un radical heterociclilo según se ha definido,p ej , oxazol-2-ilaminometilo, 2-

(oxazol-2-ilamino)etilo, piperidin-4- ilaminometilo, 2-(piperidin-4-ilamino)etilo, y similares.

"Heterociclilcarbonilamino" hace referencia a un radical de la fórmula -N(H)-C(O)- R_g donde R_g es un radical heterociclilo según se ha definido, por ejemplo, piperidin-4-ilcarbonilamino, furan- 2-ilcarbonilamino, morfolin-4-ilcarbonilamino, y similares.

"Heterociclilcarbonilaminoalquilo" hace referencia a un radical de la fórmula - R_a-N(H)-C(O)-R_g donde R_a es un radical alquilo según se ha definido y R_g es un radical heterociclilo según se ha definido, por ejemplo, piperidin-4- ilcarbonilaminometilo, 2-(furan-2-ilcarbonilamino)etilo, 1-(morfolin-4- ilcarbonilamino)etilo, y similares.

"Mercapto" se refiere al radical -SH.

"Mercaptoalquilo" hace referencia a un radical de la fórmula - R_a-SH donde R_a es un radical alquilo según se ha definido, p.ej., mercaptometilo, 2-mercaptoetilo, 3- mercaptopropilo, 2-mercaptobutilo y similares.

"Monoalquilamino" hace referencia a un radical de la fórmula -N(H)R_a donde R_a es un radical alquilo según se ha definido, p.ej.,metilamino, etilamino, propilamino,y similares.

"Monoalquilaminoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)R_a donde cada R_a es en forma indepen-

diente un radical alquilo según se ha definido, por ejemplo, metilaminometilo, etilaminometilo, 2-(propilamino)etilo, y similares.

"(Monoalquilamino)aralquilo" hace referencia a un radical de la fórmula - R_d-N(H)R_a donde R_a es un radical alquilo según se ha definido y R_d es un radical aralquilo según se ha definido, por ejemplo, (metilamino) (fenil) metilo, 1-(etilamino)-1-(4-metoxifenil)etilo, 2- (isopropilamino)-3-(3-clorofenil)propilo, y similares.

"Monoarilamino" hace referencia a un radical de la fórmula - N(H)R_b donde R_b es un radical arilo según se ha definido, p.ej., fenilamino, (4-metoxifenil)amino, (3,4,5-trimetoxifenil) amino y similares.

"Monoarilaminoalquilo" hace referencia a un radical de la fórmula - R_a-N(H)R_b donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, por ejemplo, fenilaminometilo, 2-((4- metoxifenil)amino)etilo, 3-((3,4,5-trimetoxifenil)amino)propilo, y similares.

"Monoaralquilamino" hace referencia a un radical de la fórmula - N(H)R_d donde R_d es un radical aralquilo según se ha definido, p.ej., bencilamino, (3,4,5- trimetoxibencil)amino, (4-clorobencil)amino, y similares.

"Monoaralquilaminoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)R_d donde R_a es un radical alquilo se-

gún se ha definido y R_d es un radical aralquilo según se ha definido, p.ej., bencilaminometilo, (3- fenilpropil)aminometilo, 2-(bencilamino)etilo, y similares.

"Monoalquilaminocarbonilo" hace referencia a un radical de la fórmula $-C(O)N(H)R_a$ donde R_a es un radical alquilo según se ha definido, por ejemplo, metilaminocarbonilo, etilaminocarbonilo, propilaminocarbonilo, y similares

"Monoalquilaminocarbonilalquilo" hace referencia a un radical de la fórmula $-R_a-C(O)N(H)R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., metilaminocarbonilmetilo, 2- (etilaminocarbonil)etilo, 3-(propilaminocarbonil)propilo, y similares.

"Monoarilaminocarbonilo" hace referencia a un radical de la fórmula $-C(O)\ N(H)R_b$ donde R_b es un radical arilo según se ha definido, por ejemplo, fenilaminocarbonil,(3,4,5-*tris*(trifluorometoxi)fenil)-aminocarbonilo, (4-clorofenil) aminocarbonilo, y similares

"Monoarilaminocarbonilalquilo" hace referencia a un radical de la fórmula $-R_a-C(O)N(H)R_b$ donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, por ejemplo, fenilaminocarbonilmetilo, 2-((4-clorofenil) aminocarbonil)etilo, 3-((3,4,5-trimetoxifenil)aminocarbonil)propilo, y similares

"Monoaralquilaminocarbonilo" hace referencia a un radical de la fórmula $-C(O)N(H)R_d$ donde R_d es un radical aralquilo

según se ha definido, por ejemplo, bencilaminocarbonilo, (3,4,5-tris(trifluorometoxi)bencil)-aminocarbonilo, (4-clorobencil) aminocarbonilo, y similares

"Monoaralquilaminocarbonilalquilo" hace referencia a un radical de la fórmula $-R_a-C(O)N(H)R_d$ donde R_a es un radical alquilo según se ha definido y R_d es un radical aralquilo según se ha definido, p ej., bencilaminocarbonilmetilo, 2-((4-clorobencil) aminocarbonil)etilo, 3-((3,4,5-trimetoxibencil)aminocarbonil)propilo, y similares

"(Monoalquilaminocarbonilalquil)aminocarbonilo" hace referencia a un radical de la fórmula $-C(O)-N(H)-R_a-C(O)-N(H)R_a$ donde cada R_a es en forma independiente un radical alquilo según se ha definido, p.ej., (metilaminocarbonilme-til)aminocarbonilo, (2-(metilaminocarbonil)etil)aminocarbonilo, (1-(etilaminocarbonil)etil) aminocarbonilo, y similares.

"Monoalquilalaninamido" se refiere un radical de la fórmula $-N(H)-C(O)-C(CH_3)H-N(H)R_a$ donde R_a es un radical alquilo según se ha definido y el nitrógeno unido se designa como "*N*" y el otro nitrógeno (con el sustituyente R_a) se designa como "*N*", por ejemplo, *N'*-metilalanimido, *N'*-etilalanimido, y similares

"Monoalquilglicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(H)\ R_a$ donde R_a es un radical alquilo según se ha definido y el nitrógeno de unión se

designa como "*N*" y el otro nitrógeno (con el sustituyente R_a) se designa como "*N*", por ejemplo, *N'*-metilglicinamido *N'*-etilglicinamido, y similares.

"(Monoarilaminocarbonil) glicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(H)-C(O)-N(H)R_b$ donde R_b es un radical arilo según se ha definido, por ejemplo, ((4- fenoxifenil)aminocarbo-nil)glicinamido, ((4-clorofenil)aminocarbonil) glicinamido, (fenilaminocarbonil)glicinamido, y similares

"(Monoarilaminocarbonil)(alquil)glicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(R_a)-C(O)-N(H)R_b$ donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido y el nitrógeno al cual R_a está unido se designa como "*N*", p ej., ((4-fenoxifenil) aminocarbonil)(*N'*-metil)glicinamido, ((4-clorofenil) aminocarbonil)(*N'*-etil)glicinamido, (fenilaminocarbonil)(*N'*-metil)glicinamido, y similares.

"(Monoaralquilaminocarbonil)glicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(H)-C(O)-N(H)R_d$ donde R_d es un radical aralquilo según se ha definido, por ejemplo, ((4-fenoxibencil)aminocarbonil)glicinamido, ((4-clorobencil)aminocarbonil)glicinamido, (bencilaminocarbonil)glicinamido, y similares

"(Monoaralquilaminocarbonil)(alquil)glicinamido" hace referencia a un radical de la fórmula $-N(H)-C(O)-CH_2-N(R_a)-$

C(O)- N(H)R_d donde R_a es un radical alquilo según se ha definido y R_d es un radical aralquilo según se ha definido y el nitrógeno al cual el R_a está unido se designa como "*N*",p ej., ((4-fenoxibencil)aminocarbonil)(*N'*-metil) glicinamido, ((4-clorobencil)aminocarbonil)(*N'*-etil)glicinamido, (bencilaminocarbonil)(*N'*-metil)glicinamido, y similares.

"Monoalquilureido" hace referencia a un radical de la fórmula -N(H)-C(O)-N(H) R_a o un radical de la fórmula -N(R_a)-C(O)-NH_2 donde R_a es un radical alquilo según se ha definido y el nitrógeno de unión se designa como " *N*" y el otro nitrógeno se designa como "*N*", por ejemplo, *N'*-metilureido, *N'*-etilureido, *N'*- propilureido, *N*-metilureido, *N*-etilureido, *N*- propilureido, y similares.

"Monofenilureido" hace referencia a un radical de la fórmula -N(H)-C(O)-N(H)R_h donde R_h es un radical fenilo según se ha definido, y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*", por ejemplo, *N'*-fenilureido, *N'*-(4- nitrofenil)ureido, *N'*-(3-clorofenil)ureido, y similares

"Monobencilureido" hace referencia a un radical de la fórmula -N(H)-C(O)-N(H)- CH_2-R_h donde R_h es un radical fenilo según se ha definido, y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como " *N*"', por ejemplo, *N'*-bencilureido, *N'*-(4-nitrobencil)

ureido, *N'*-(3-clorobencil)ureido, y similares.

"Monohaloalquilureido" hace referencia a un radical de la fórmula -N(H)-C(O)-N(H) R_f o un radical de la fórmula -N(R_f)-C(O)-NH_2 donde R_f es un radical haloalquilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N* ",p.ej., *N'*-clorometilureido, *N'*-(2,2- difluoroetil)ureido, *N'*-(3-cloropropil)ureido, *N*- (trifluorometil)ureido, *N*-(pentafluoroetil)ureido, *N*-(3- iodopropil)ureido, y similares.

"Monoarilureido" hace referencia a un radical de la fórmula -N(H)-C(O)-N(H)R_b o un radical de la fórmula -N(R_b) -C(O)-NH_2 donde R_b es un radical arilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*", por ejemplo, *N'*-fenilureido, *N'*-(4-metoxifenil)ureido, *N'*-(3-clorofenil)ureido, *N*-fenilureido, *N*-(2-trifluorometilfenil)ureido, *N*-(4-clorofenil) ureido, y similares

"Monoaralquilureido" hace referencia a un radical de la fórmula -N(H)-C(O)-N(H)R_d o un radical de la fórmula -N(R_d) -C(O)-NH_2 donde R_d es un radical aralquilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*", por ejemplo, *N'*-bencilureido, *N'*-(4-metoxibencil) ureido, *N'*-(3- clorobencil)ureido, *N*-bencilureido, *N*-(2- trifluorometilbencil)ureido, *N*-(4-clorobencil)ureido, y similares.

"(Monoalquil)(monoaril)ureido" hace referencia a un radical de la fórmula $-N(R_a)-C(O)-N(R_b)H$, o un radical de la fórmula $-N(R_b)-C(O)-N(R_a)H$, o un radical de la fórmula $-N(H)-C(O)-N(R_a)(R_b)$ donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido, y donde y el nitrógeno de unión se designa como "*N* " y el otro nitrógeno se designa como "*N*", por ejemplo, *N*-metil- *N'*-fenilureido, *N*-fenil-*N'*-etilureido, *N*-metil-*N'*-(4-fluorofenil)ureido, *N'*-etil-*N'*-(3- cianofenil)ureido, y similares

"Monoalquilureidoalquilo" hace referencia a un radical de la fórmula $-R_a-N(H)-C(O)-N(H)R_a$ o un radical de la fórmula $-R_a-N(R_a)-C(O)-NH_2$ donde R_a es un radical alquilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*", por ejemplo , *N'*-metilureidometilo, 2-(*N'*- etilureido)etilo, 1-(*N'*-propilureido)etilo, *N*- metilureidometilo, 2-(*N*-etilureido)etilo, 1-(*N*- propilureido)etilo, y similares.

"Monohaloalquilureidoalquilo" hace referencia a un radical de la fórmula $-R_a-N(H)-C(O)-N(H)R_f$ o un radical de la fórmula $-R_a-N(R_f)-C(O)-NH_2$ donde R_a es un radical alquilo según se ha definido y R_f es un radical haloalquilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*"', p.ej., *N'*- clorometilureidometilo, 2-(*N'*-(2,2-difluoro-

etil)ureido)etilo, 1- (*N'*-(3-cloropropil)ureido)etilo, *N*-(trifluorometil) ureidometilo, 2-(*N*-(pentafluoroetil)ureido)etilo, 1-(*N*-(3- iodopropil)ureido)etilo, y similares.

"Monoarilureidoalquilo" hace referencia a un radical de la fórmula $-R_a-N(H)-C(O)-N(H)\ R_b$ o un radical de la fórmula $-R_a\ -N(R_b)-C(O)-NH_2$ donde R_a es un radical alquilo según se ha definido y R_b es un radical arilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*", por ejemplo, *N'*-fenilureidometilo, 2-(*N'*-(4- metoxifenil)ureido)etilo, 1-(*N'*-(3-clorofenil)ureido)etilo, *N*-fenilureidometilo, 2-(*N*-(2-trifluorometilfenil)ureido) etilo, 1-(*N*-(4-clorofenil)ureido)etilo, y similares

"Monoaralquilureidoalquilo" hace referencia a un radical de la fórmula $-R_a\ -N(H)-C(O)-N(H)R_d$ o un radical de la fórmula $-R_a-N(R_d)-C(O)-NH_2$ donde R_a es un radical alquilo según se ha definido y R_b es un radical aralquilo según se ha definido y el nitrógeno de unión se designa como "*N*" y el otro nitrógeno se designa como "*N*", p.ej , *N'*-bencilureidometilo, 2-(*N'*-(4-metoxibencil)ureido)etilo, 1-(*N'*-(3-clorobencil)ureido)etilo, *N*- bencilureidometilo, 2- (*N*-(2-trifluorometilbencil)ureido)etilo, 1-(*N*-(4- clorobencil)ureido)etilo, y similares

"Monofenilamino" hace referencia a un radical amino susti-

tuido por un radical fenilo según se define en la presente.

"Monofenilalquilamino" hace referencia a un radical amino sustituido por un grupo fenilalquilo según se define más adelante p.ej ,bencilamino, 2-(bencil)butilamino, y similares.

"Monofenilaminoalquilo" hace referencia a un radical alquilo según se ha definido sustituido por un grupo monofenilamino según se ha definido, por ejemplo, (fenilamino)metilo, 2-(1-(fenil)etilamino) etilo, y similares.

"Monofenilalquilaminoalquilo" hace referencia a un radical alquilo según se ha definido sustituido por un grupo monofenilalquilamino según se ha definido, p.ej., (bencilamino)metilo, 2-(2-bencil)butilamino)etilo, y similares.

"Nitro" se refiere al radical $-NO_2$.

"Oxo" hace referencia al sustituyente =O

"opcional" u "opcionalmente" significa que las circunstancias que se describen a continuación pueden ocurrir o no, y que la descripción incluye instancias en las que dicho evento o circunstancia ocurre e instancias en las cuales no ocurre. Por ejemplo, "arilo opcionalmente sustituido" significa que el radical arilo puede estar sustituido o no y que la descripción incluye tanto radicales arilo sustituidos como radicales arilo sin sustitución alguna.

"Fenilo" hace referencia al radical benceno que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, alquilo, haloalquilo, alcoxi, alquenilo, nitro, ciano, amino, monoalquilamino, dialquilamino, alquilcarbonilo, carboxi, alcoxicarbonilo, y aminocarbonilo.

"Fenoxi" se refiere al radical de la fórmula $-OR_h$ donde R_h es fenilo según se ha definido.

"Fenilalquilo" hace referencia a un radical alquilo según se ha definido sustituido por un radical fenilo, por ejemplo, bencilo, y similares.

"Fenilalquenilo" hace referencia a un radical alquenilo según se ha definido sustituido por un radical fenilo, por ejemplo, 3-fenilprop-2-enilo, y similares.

"Fenilalcoxi" hace referencia a un radical de la fórmula $-OR_1$ donde R_1 es un radical fenilalquilo según se ha definido, por ejemplo, benciloxi, y similares.

"Fenilalcoxialquilo" hace referencia a un radical alquilo según se ha definido sustituido por un radical fenilalcoxi según se ha definido, por ejemplo, benciloximetilo, y similares

"Fenilcarbonilo" hace referencia a un radical de la fórmula $-C(O)-R_h$ donde R_h es un radical fenilo según se ha definido, por ejemplo, (4-clorofenil) carbonilo, (4-fluorofenil)carbonilo, y similares.

"Fenilaminocarbonilo" hace referencia a un radical de la fórmula -C(O)-N(H)-R_h donde R_h es un radical fenilo según se ha definido, p.ej., (4-clorofenil)aminocarbonilo, (4- metoxifenil)aminocarbonilo, y similares.

"Contraión aceptable para uso farmacéutico" hace referencia los anions que retienen la eficacia biológia y las propiedades del compuesto madre que no sean indeseables desde el punto de vista biológico o de otra índole. Ejemplos de tales aniones se pueden encontrar en Berge, S M. *et al*, *Journal de Pharmaceutical Sciences* (1977), Vol. 66, No. 1, pp 1-19.

"Sal aceptable para uso farmacéutico" incluye sales de adición ácida y básica.

"Sal de adición ácida aceptable para uso farmacéutico" hace referencia a las sales que retienen la eficacia biológica y las propiedades de las bases libres, que no son indeseables desde el punto de vista biológico o de otra índole, y que se forman con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido bromídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares, y ácidos orgánicos tal como ácido acético, ácido propiónico, ácido pirúvico, ácido maleico, ácido malónico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido mandélico, ácido metansulfónico, ácido etansulfónico, ácido *p*-

toluensulfónico, ácido salicílico, y similares.

"Sal de adición básica aceptable para uso farmacéutico" hace referencia a las sales que retienen la eficacia biológica y propiedades de los ácidos libres, que no son indeseables desde el punto de vista biológico ni de otra índole Estas sales se preparan a partir de la adición de una base inorgánica o una base orgánica al ácido libre Las sales derivadas de bases inorgánicas incluyen, sin carácter taxativo, las sales de sodio, potasio, lirio, amonio, calcio, magnesio, zinc, aluminio y similares. Las sales inorgánicas preferidas son las de amonio, sodio, potasio, calcio y magnesio Las sales derivadas de bases orgánicas incluyen, sin carácter taxativo, sales de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas sustituidas existentes en la naturaleza, aminas cíclicas y resinas de intercambio iónico básicas, tal como isopropilamina, trimetilamina, dietilamina, trietilamina, tripropilamina, etanolamina, 2-dimetilaminoetanol, 2- dietilaminoetanol, trimetamina, diciclohexilamina, lisina, arginina, histidina, cafeína, procaína, hidrabamina, colina, betaina, etilendiamina, glucosamina, metilglucamina, teobromina, purinas, piperazina, piperidina, *N*- etilpiperidina, resinas de poliamina y similares Las bases orgánicas particularmente preferidas son isopropilamina, dietilamina,

etanolamina, trimetilamina, diciclohexilamina, colina y cafeína.

"THF" hace referencia a tetrahidrofurano

"Cantidad eficaz en términos terapéuticos" hace referencia a la cantidad de un compuesto de fórmula (I) que, al administrarse a un humano de sexo femenino que necesita dicha administración, es suficiente para efectuar el tratamiento, según se define más adelante, de la endometrosis que se alivia por la actividad antagonista de CCR-1. La cantidad de un compuesto de fórmula (I) que constituye una "cantidad eficaz en términos terapéuticos" variará según el compuesto, el trastorno y su gravedad, y la edad del humano de sexo femenino a tratar, pero se puede determinar en forma rutinaria por un especialista en la materia en base a sus propios conocimiento y la presente memoria descriptiva.

"Tratar" o "tratamiento" según se utilizan en la presente se refieren al tratamiento de la endometrosis en un humano de sexo femenino; e incluyen·

(i) prevenir el trastorno en un humano de sexo femenino, en particular, cuando dicha persona de sexo femenino tiene predisposición a adquirirlo pero aún no se le ha diagnosticado;

(ii) inhibir el trastorno, es decir, detener su desarrollo, o

(iii) aliviar el trastorno, es decir, causar la regresión del trastorno

"Ureido" hace referencia a un radical de la fórmula -N(H)-C(O)-NH_2.

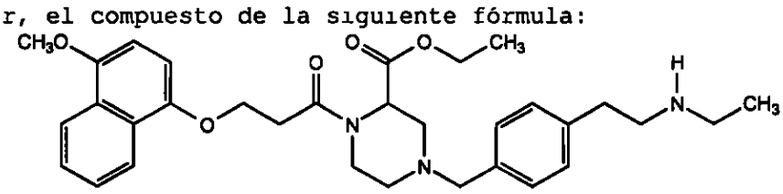
"Ureidoalquilo" hace referencia a un radical de la fórmula -R_a-N(H)C(O)NH_2 donde R_a es un radical alquilo según se ha definido, por ejemplo, ureidometilo, 2- (ureido)etilo, 3-(ureido)propilo, y similares.

Queda entendido a partir de las definiciones y ejemplos precedentes que para los radicales que contienen un grupo alquilo sustituido, cualquier sustitución puede producirse sobre cualquier carbono del grupo alquilo del grupo alquilo.

Los compuestos de la invención, o su sal aceptable para uso farmacéutico, pueden tener átomos de carbono asimétricos en su estructura. Los compuestos de la invención y su sal aceptable para uso farmacéuticos por lo tanto pueden existir como estereoisómeros simples, racematos, y como mezclas de enantiómeros y diastereómeros Todos dichos estereoisómeros simples, racematos y mezclas de los mismos se consideran dentro del alcance de esta invención. La configuración absoluta de algunos átomos de carbono dentro de los compuestos, si es conocida, se indica por medio de los descriptores absolutos apropiados *R* o *S* El descriptor " *trans*" se utiliza para indicar que los sustituyentes R^{1a} o R^{1b} están

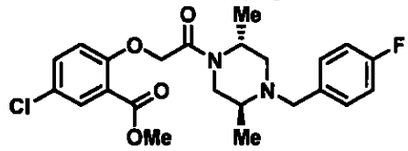
en los lados opuestos del plano de la piperazina. El descriptor "*cis*" se utiliza para indicar que los sustituyentes R^{1a} o R^{1b} están del mismo lado que el plano de la piperazina.

La nomenclatura utilizada en la presente es una forma modificada del sistema I U.P A C. en el cual los compuestos de la invención se denominan derivados de piperazinaon. Por ejemplo, un compuesto de fórmula (la) en donde R^6 es -C(O)-, R^5 es etileno, R^4 es -O-, R^{1a} está en la posición 2 del anillo piperazina y es etoxicarbonilo, R^2 es 2-(etilamino)etilo en la posición 4 del anillo fenilo y R^3 es naftalen-1-ilo sustituido en la posición 4 por metoxi, es decir, el compuesto de la siguiente fórmula:



acá se denomina 1-(2-((4-metoxinaftalen-1-il)oxi)etil)carbonil-2- etoxicarbonil-4-(4-(2-(etilamino)etil)bencil)piperazina o con la nomenclatura de acuerdo con el siguiente ejemplo:

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico



. Utilidad y Administración

A. Utilidad

Los antagonistas del CCR1 de acuerdo con la presente invención son potentes inhibidores de la incidencia de enfermedad en modelos animales y modelos de cultivos celulares de la endometrosis.

Los compuestos de la invencion inhiben la migración de monocitos y macrófagos inducida por quimioquinas (MIP-1α y RANTES) y por lo tanto son útiles en el tratamiento y prevención de la endometrosis en mujeres

Se llevaron a cabo estudios clínicos para investigar el beneficio de los antagonistas del CCR1 de acuerdo con la presente invención en el tratamiento y prevención de la endometrosis.

B. Pruebas

Se pueden emplear varios ensayos para demostrar que los compuestos inhiben la actividad de MIP-1α o RANTES. Un ensayo utiliza un microfisiómetro, que utiliza un sensor potenciométrico orientable hacia la luz a base de silicio patentado para monitorear de manera continua cambios sutiles de los niveles de pH extracelular Dichos cambios son resultado de la generación de metabolitos ácidos excretados por las células vivas en su microambiente inmediato durante condiciones basales y de estímulo Anteriormente se había demostrado por microfisiometría que las células THP-1, que se ha mostrado que expresan los receptores de quimioquina CCR1 y

CCR2, responden respondiendo a la dosis a sus respectivas quimioquinas, que incluyen MIP-1α, RANTES y MCP-1 (un ligando para CCR2) Véase, *p.ej.*, Hirst, M. Et *al.*, "Chemokine receptors", *Journal of NIH Research* (1995), Vol. 80.

Otro ensayo que se puede utilizar para demostrar la capacidad de los compuestos de inhibir la actividad de MIP-1α y RANTES se basa en la medición de las concentraciones intracelulares de Ca^{2+} y/o los aumentos de intracelular liberación de fosfato de [^{3}H]inositol desde células estimuladas por MIP-1α y RANTES. Los ligandos que se unen al receptor CCR1 causan la activación de fosfolipasa C inducida por proteína G, que lleva a la conversión de fosfato de fosfatidil inositol a fosfato de inositol y diacilglicerol A su vez el fosfato de inositol se une a un receptor situado en sitios intracelulares que liberan Ca^{2+} dentro del citoplasma. Además de los aumentos de concentración de Ca^{2+} debidos a la liberación desde los depósitos intracelulares, la unión del fosfato de inositol a su receptor produce un aumento del flujo de calcio extracelular a través de la membrana y hacia el interior de la célula. De esa manera, la activación del receptor CCR1 por MIP-1α y RANTES y la subsiguiente inhibición de la activación por los compuestos de la invención se puede determinar haciendo ensayos para buscar un aumento de los niveles intracelulares de Ca^{2+} libre. Típicamente, esto se puede conseguir utilizando sondas fluorescentes sensibles al

calcio como por ejemplo quin-2, fura-2 e indo-1. Como alternativa, la activación funcional o la inhibición de la activación del receptor CCR1 se puede medir por cuantificación de la liberación de fosfato de [^{3}H]inositol desde la célula premarcada con [^{3}H]inositol.

Se pueden emplear ensayos estándar de unión *in vitro* para demostrar la afinidad de los compuestos por el receptor CCR1 (inhibiendo de esa manera la actividad de MIP-1α y RANTES por unión competitiva al receptor). Véase, *por ejemplo,* Neote, K. E*t al.*, Cell (1993), Vol. 72, pp. 415-425. Un ensayo en particular emplea células HEK293 transfectadas de manera estable para expresar el receptor CCR1 humano

Los modelos de endometrosis de cultivos celulares con células U937 humanas y macrófagos peritoneales humanos primarios en combinación con una mezcla de fluido peritoneal proveniente de pacientes con endometrosis se utilizan como herramientas para investigar los efectos de los antagonistas del CCR1 sobre la inhibición y la reducción de la migración de monocitos/macrófagos inducida por quimioquina.

La determinación del mARN de CCR1 en muestra de tejido endometrial y endometriósico se puede realizar p ej mediante análisis cuantitativo RT-PCR en tiempo real.

Los ensayos *in vivo* estándar que se pueden emplear para demostrar la utilidad de los compuestos en el tratamiento de la endometrosis son p.ej el modelo animal de endometrosis

inducida quirúrgicamente en intacta ratas que atraviesan un ciclo según se informó también en la literatura (15).

Otros modelos muy importantes para evaluar la utilidad *in vivo* de los compuestos en el tratamiento de la endometrosis son los modelos en primates.

En comparación con los roedores, los primates (Babuino, Cynomolgous, monos Rhesus) tienen un ciclo menstrual, se reproducen de manera continua y desarrollan endometrosis espontánea. Además, la endometrosis también se puede inducir por ejemplo por la inoculación de tejido menstrual o por transplante autólogo de tejido endometrial dentro de la cavidad peritoneal (9, 10) Además es posible aislar y caracterizar su fluido peritoneal

Los datos experimentales de los investigadores muestran por ejemplo que los primates no humanos expresan el receptor CCR1. Como en los humanos, podrían mostrar que el CCR1 se localiza en las células inmunes que infiltran el tejido en lesiones endometriósicas/injertos. Utilizando tinción inmunohistoquímica y conteo de células se podría demostrar que el número de las células CCR1 positivas está regulado de manera ascendente en injertos endometriósicos de mono Rhesus (véase la figura 6) La ventaja del modelo de primate no humano es la morfología de las lesiones endometriósicas (lesiones rojas, lesiones blancas, endometrioma) que se parecen a aquellas que se encuentran en mujeres y reflejan la situa-

ción humana. Se llevaron a cabo estudios en primates no humanos para evaluar la actividad del antagonista del CCR1 de acuerdo con la presente invención

C. Administración general

La administración de los compuestos de la invención, o sus sales aceptables para uso farmacéutico, en forma pura o en una composición farmacéutica apropiada, se puede llevar a cabo mediante cualquiera de los modos de administración o agentes aceptados para servir a utilidades similares. Por lo tanto, la administración puede ser, p ej., por vía oral, nasal, parenteral, tópica, transdérmica, o rectal, sublingual, intramuscular, subcutánea, intravaginal o intravenosa en formas de dosificación sólidas, semisólidas, de polvo liofilizado, o líquidas, como p ej , tabletas, supositorios, píldoras, cápsulas de gelatina blanda elásticas y duras, polvos, soluciones, suspensiones, o aerosoles, etcétera, preferiblemente en formas de dosificación unitaria apropiadas para la administración simple de dosificaciones precisas. Las composiciones incluirán un vehículo farmacéutico o excipiente convencional y un compuesto de la invención como el/un agente activo,y,además, pueden incluir otros agentes medicinales, agentes farmacéuticos, vehículos, coadyuvantes, etc.

En general, dependiendo del modo de administración que se desee emplear, las composiciones aceptables para uso farmacéutico contendrán entre aproximadamente 1% y aproximada-

mente 99% en peso de un(unos) compuesto(s) de la invención, o una sal de los mismos aceptable para uso farmacéutico, y entre 99% y 1% en peso de uno o más excipiente(s) farmacéutico(s) apropiado(s). Preferiblemente, la composición tendrá entre aproximadamente 5% y 75% en peso de un(unos) compuesto(s) de la invención, o una sal de los mismos aceptable para uso farmacéutico, donde el resto son excipientes farmacéuticos apropiados.

La ruta de administración preferida es la oral, utilizando un régimen conveniente de dosificación diaria que se puede ajustar de acuerdo con el grado de gravedad del estado de enfermedad que se debe tratar. Para dicha administración oral, una composición aceptable para uso farmacéutico que contiene un(unos) compuesto(s) de la invención, o una sal de los mismos aceptable para uso farmacéutico, se forma mediante la incorporación de cualquiera de los excipientes que se emplean normalmente.Dichos excipientes incluyen cargas, aglutinantes, desintegrantes, soluciones amortiguadoras de pH, conservantes, antioxidantes, lubricantes, saborizantes, espesantes, agentes colorantes, emulsionantes, etcétera, no tóxicos y químicamente compatibles,p.ej.,los grados farmacéuticos de manitol, lactosa, almidón, almidón pregelatinizado, estearato de magnesio, sacarina sódica, talco, derivados de éter de celulosa, glucosa, gelatina, sacarosa, citrato, ciclodextrina, galato de propilo, etcétera Dichas com-

posiciones toman la forma de soluciones, suspensiones, tabletas, píldoras, cápsulas, polvos, formulaciones de liberación sostenida etc.

Preferiblemente, dichas composiciones tomarán la forma de una cápsula, caplet o comprimido y por lo tanto también contendrán un diluyente como p ej lactosa, sacarosa, fosfato dicálcico, etcétera; un desintegrante como por ejemplo croscaramelosa sódica o derivados de los mismos, un lubricante como por ejemplo estearato de magnesio, etcétera, y un aglutinante como p.ej. un almidón, goma de acacia, polivinilpirrolidona, gelatina,derivados de éter de celulosa, etc.

Los compuestos de la invención o sus sales aceptables para uso farmacéutico también se pueden formular en un supositorio utilizando, por ejemplo, entre aproximadamente 0,5% y aproximadamente 50% de ingrediente activo dispuesto en un vehículo que se disuelve lentamente dentro del cuerpo, *por ejemplo*, polioxietilenglicoles y polietilenglicoles (PEG), *p. ej.*, PEG 1000 (96%) y PEG 4000 (4%), y propilenglicol.

Las composiciones líquidas para administrar en uso farmacéutico se pueden preparar, por ejemplo, disolviendo, dispersando, etc., un(unos) compuesto(s) de la invención (entre aproximadamente 0,5% y aproximadamente 20%), o una sal de los mismos aceptable para uso farmacéutico, y coadyuvantes farmacéuticos opcionales en un vehículo, como p.ej., agua, solución salina, dextrosa acuosa,ciclodextrina acuosa, gli-

cerol, etanol etc,para formar así una solución o suspensión.

Si se desea, una composición farmacéutica de la invención también puede contener cantidades minoritarias de sustancias auxiliares como p.ej. agentes humectantes o emulsionantes,agentes amortiguadores de pH,antioxidantes, etc.,como p.ej.,ácido cítrico, monolaurato de sorbitán, oleato de trietanolamina, hidroxitolueno butilado, etc.

Los métodos que se emplean en efecto para preparar dicha formas de dosificación se conocen, o serán evidentes, para aquellos con experiencia en el arte, p.ej., véase *Remington's Pharmaceutical Sciences,* 18va Ed., (Mack Publishing Company, Easton, Pennsilvania, 1990). En todo caso, la composición que se va a administrar contendrá una cantidad efectiva para uso terapéutico de un compuesto de la invención, o una sal del mismo aceptable para uso farmacéutico, para el tratamiento de la edometriosis aliviada por la inhibición de la actividad de las quimioquinas,MIP-1α y RANTES.

Los compuestos de la invención, o sus sales aceptables para uso farmacéutico, se administran en una cantidad efectiva para uso terapéutico que variará dependiendo de una variedad de factores que incluyen la actividad del compuesto específico que se emplee, la estabilidad metabólica y longitud de acción del compuesto, la edad, peso corporal, salud general, sexo, dieta, modo y tiempo de administración, tasa

de excreción, combinación de drogas, la gravedad de los estados de enfermedad en particular, y del huésped sometido a terapia. En general, una dosis diaria efectiva para uso terapéutico es entre aproximadamente 0,014mg y aproximadamente 14,0mg/kg de peso corporal por día de un compuesto de la invención, o una sal del mismo aceptable para uso farmacéutico; preferiblemente, entre aproximadamente 0,14mg y aproximadamente 10,0mg/kg de peso corporal por día, y aún más preferiblemente, entre aproximadamente 1,4mg y aproximadamente 7,0mg/kg de peso corporal por día Por ejemplo, para administrar a una persona de 70kg, el rango de dosificación sería entre aproximadamente 1,0mg y aproximadamente 1,0 gramo por día de un compuesto de la invención, o una sal del mismo aceptable para uso farmacéutico, preferiblemente entre aproximadamente 10mg y aproximadamente 700mg por día, y aún más preferiblemente entre aproximadamente 100mg y aproximadamente 500mg por día

Descripción de las figuras

Otras características y ventajas de la invención se harán evidentes de la siguiente descripción de algunas formas favorables de formas de realización de la invención, que se dan como ejemplos puramente no restrictivos, con referencia a las figuras adjuntas, donde

La figura 1 muestra la localización del CCR1 en lesiones endometriósicas y tejido endometrial.

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En lesiones endometriósicas-peritoneales el receptor de quimioquina CCR1 se localiza en células inmunes que infiltran el tejido (A-D). No se detectaron células inmunes que expresan CCR1 en el endometrio de pacientes con endometrosis (E) así como en el endometrio de controles no endometriósicos (G). Control negativo (F, H).

La figura 2 muestra los datos del análisis de la expresión de mARN de CCR1 en lesiones endometriósicas y en endometrio proveniente de pacientes con endometrosis.

Controles: Las líneas 1, 2 y 3 representan el endometrio proveniente de mujeres no endometriósicas. En dichas muestras de tejido la expresión de mARN de CCR1 es baja. Las bandas 4-9 son muestras de tejido provenientes de mujeres con endometrosis.

Entre paréntesis: endometrio y lesión endometriósica proveniente del mismo paciente.

La expresión de mARN de CCR1 está sensibilizada en las lesiones endometriósicas (líneas 5, 7, 9) en comparación con la muestra de endometrio (líneas 4, 6, 8)

La figura 3 muestra la caracterización de células inmunes que expresan CCR1.

Las co-inmunotinciones con anticuerpos monoclonales para CCR1 (Figs. A y D), CD4 (Fig 4B) y CD68 (Fig. 4E) confirman que el receptor de quimioquina CCR1 se expresa en monocitos, y macrófagos (CD 68) células T ayudantes (CD4)

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(Figs 4C y F).

La figura 4 muestra los efectos del antagonista del CCR1 sobre el área y el volumen de lesiones endometriósicas peritoneales en ratas con endometrosis inducida experimental

Controles barra blanca: los animales se trataron durante 4 semanas con vehículo, propilenglicol (0,5mg/kg). Barra punteada: Los animales recibieron un antiestrógeno (11β-Fluoro-7α-(14,14,15,15,15-pentafluoro-6-metil-10-tia-6-aza-pentadecil)estra-1,3,5(10)-trieno-3,17β-diol) (1mg/kg). Barra rayada· Los animales se trataron con una antagonista del CCR1 de acuerdo con la presente solicitud y en particular con (2*R*)-1-{[4-cloro-2-(ureido)fenoxi]metil}carbonil-2-metil-4-(4-fluorobencil)piperazina como sal sulfato (50mg/kg) En comparación con el control de vehículo, los datos muestran que los compuestos de acuerdo con la presente invención reducen los efectos sobre el área y el volumen de quistes endometriósicos peritoneales en ratas.

Las figuras 5a y 5b muestran la expresión de mARN de CCR1 en el modelo de endometrosis en ratas.

La figura 5a muestra la expresión del mARN de CCR1 en quistes endometriósicos de mesenterio y peritoneo Como controles se utilizaron úteros de rata y ovarios de rata operados (1-3 animal 1; 4-7 animal 2) En comparación con los úteros y ovarios, la expresión de mARN de CCR1 se ve sensi-

bilizada en los quistes de peritoneo y mesenterio.

La figura 5b muestra la expresión del ligando RANTES de CCR1 en animales tratados y no tratados. Grupo de control (animales no tratados): alta expresión de RANTES en lesiones mesenteriales y peritoneales. Después de 3 semanas de tratamiento, el tratamiento con antagonistas del CCR1 induce una significativa regulación descendente del mARN de RANTES en quistes peritoneales y mesenteriales en ratas. Los resultados representan los valores promedio de tres animales.

Figuras 6a y 6b· número y localización de células con el CCR1 teñido en el endometrio e injertos/lesiones endometriósicas de mono Rhesus

Figura 6A: conteos positivos para CCR1 en células. Los conteos de células representan el número promedio de las células CCR1 positivas por sección contada con una grilla ocular. Las células se identificaron por tinción inmunohistoquímica. En seis secciones se contaron n= 3 animales El número de células que expresan CCR1 está regulado de manera ascendente en los injertos endometriósicos durante el ciclo menstrual en monos Rhesus

Figura 6b: Localización de las células con el CCR1 teñido en injertos/lesiones endometriósicos y en el endometrio. En comparación con el endometrio, el número de células que expresan CCR1 se ve aumentado en los injertos/lesiones endometriósicos.

Realizaciones preferidas

Un aspecto de la invención son los compuestos de fórmula (Ia) según se ha definido en el resumen de la invención de estos compuestos, un grupo preferido de compuestos de fórmula (Ia) es el grupo de compuestos en donde

R^3 es

un sistema de anillo carbocíclico sustituido por uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, alquilo, mercapto, mercaptoalquilo, alquiltio, alquilsulfinilo, alquilsufonilo, arilsulfonilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, alcoxi, hidroxialcoxi, ariloxi, haloalquilo, formilo, formilalquilo, nitro, nitroso, ciano, aralcoxi, haloalcoxi, aminoalcoxi, cicloalquilo, cicloalquilalquilo, (hidroxi) cicloalquilalquilo, cicloalquilamino, cicloalquilaminoalquilo, cianoalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, hidroxialquilo, (hidroxi) aralquilo, (monoalquilamino)aralquilo, (hidroxialquil)hioalquilo, hidroxialquenilo, hidroxialquinilo, alcoxialquilo, (alcoxi)aralquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, aminoalquilamino, heterociclilamino, (cicloalquilalquil)amino, alquilcarbonilamino, alcoxicarbonilamino, alquenilcarbonilamino, cicloal-

quilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, (alcoxicarbonil)(alquil)amino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, hidroxialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, (cicloalquialquil) aminoalquilo, alcoxicarbonilaminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil)(alquil)aminoalquilo, heterociclilaminoalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, arilcarbonilo, aralquilcarbonilo, (hidroxialcoxi)carbonilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, alcoxialquilcarboniloxialquilo, dialquilaminocarboniloxialquilo, alquilcarbonilalquilo, arilcarbonilalquilo, aralquilcarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, (aminocarbonilalquil) aminocarbonilo, (monoalquilaminocarbonilalquil) aminocarbonilo, (carboxialquil) aminocarbonilo, (alcoxicarbonilalquil)aminocarbonilo, (aminoalquil)

aminocarbonilo, (hidroxialquil)aminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, amidino, hidroxiamidino, guanidino, ureido, monoalquilureido, monoarilureido, monoaralquilureido, monohaloalquilureido, (monoalquil)(monoaril)ureido, dialquilureido, diarilureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil) ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil) glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil)glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil)glicinamido, (monoaralquilaminocarbonil)(alquil)glicinamido, (monoarilaminocarbonil) glicinamido, (monoarilaminocarbonil)(alquil)glicinamido, glicinamidoalquilo, alaninamido, monoalquilalaninamido, alaninamidoalquilo, heterociclilo y heterociclilalquilo.

De este grupo de compuestos, un subgrupo preferido de compuestos es el grupo de compuestos en donde:

R^4 es

-O-, -N(R^7)- o -C(R^8)-;

R^5 es

una cadena alquileno;

R^7 es

seleccionado del grupo formado por hidrógeno, alquilo, arilo, aralquilo, alquilcarbonilo, alquilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, y alcoxicarbonilo, y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, alquilo, arilo, aralquilo, hidroxi, alcoxi, hidroxialquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, alquilcarbonilamino, cicloalquilcarbonilamino, cicloalquilalquilcarbonilamino, alcoxicarbonilamino, alquilsulfonilamino, arilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, aralquilcarbonilamino, (aralquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, cicloalquilcarbonilaminoalquilo, alcoxicarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, aralquilcarbonilaminoalquilo, heterociclilcarbonilaminoalquilo, (aralquilcarbonil)(alquil)aminoalquilo, arilsulfonilamino, alquilsulfonilaminoalquilo, ureido, monoalquilureido, monohaloalquilureido, dialquilureido. ureidoalquilo, monoalquilureidoalquilo, dialquilureidoal-

quilo, monohaloalquilureidoalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, carboxialquilo, alcoxicarbonilalquilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, y dialquilaminocarbonilalquilo

De este subgrupo de compuestos, una clase preferida de compuestos es el grupo de compuestos en donde:

R^4 es

-O-;

R^5 es

metileno; y

R^6 es

-C(O)-.

De esta clase de compuestos, una subclase preferida de compuestos es el grupo de compuestos en donde·

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, alquilo, cicloalquilo, cicloalquilaminoalquilo, haloalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, alcoxialquilo, aralcoxialquilo, alquiltioalquilo, hidroxialquiltioalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, azidoalquilo, monoalquilureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, hidroxialquilaminoalquilo, ariloxial-

quilcarboniloxialquilo, aralcoxialquilcarboniloxialquilo, alquilcarbonilalquilo, alcoxicarbonilo, alcoxicarbonilalquilo, y heterociclilalquilo;

R^2 es

uno o más sustituyentes seleccionados del grupo formado por hidrógeno y halo;

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, alquilo, alcoxi, hidroxialcoxi, haloalquilo, formilo, nitro, ciano, aminoalcoxi, cicloalquilo, cicloalquilaminoalquilo, aralquilo, hidroxialquilo, (monoalquilamino)aralquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, monoaralquilamino, alquilcarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, (cicloalquialquil)aminoalquilo, alcoxicarbonilaminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, alquilsulfonilaminoalquilo,

(alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil) (alquil)aminoalquilo, heterociclilaminoalquilo, carboxi, alcoxicarbonilo, alquilcarbonilo, (hidroxialcoxi)carbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil) aminocarbonilo, (aminoalquil)aminocarbonilo, (hidroxialquil)aminocarbonilo, dialquilaminocarbonilalquilo, hidroxiamidino, ureido, monoalquilureido, monoarilureido, monoaralquilureido, (monoalquil)(monoaril)ureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil)ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil) glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil)glicinamido, (monoaralquilaminocarbonil)(alquil) glicinamido, (monoarilaminocarbonil)glicinamido (monoarilaminocarbonil) (alquil)glicinamido, alaninamido, heterociclilo y heterociclilalquilo.

Los compuestos preferidos dentro de esta subclase de compuestos se seleccionan del grupo formado por los siguien-

tes compuestos.

(2*S*)-1-((4-clorofenoxi) metil)carbonil-2-metil-4-(4-fluorobencil)piperazina,

1- ((fenoxi)metil)carbonil-2-etil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(metoximetil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-((acetilamino)metil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((4-fluorobencil)amino)etil)4- (4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((metil)amino)etil)-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-hidroxietil)amino)etil)-4-(4- fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-3-((((4-clorofenoxi)metil)carbonil)oxi)metil-5- metilpiperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(etoxicarbonil)piperazina,

4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-3-(metoxicarbonil)metilpiperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-

((metoxi) metil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-(metoxi)etil)piperazina;

4-(4-fluorobencil)-1- ((4-clorofenoxi)metil)carbonil-3-(2-hidroxi-2-(4-metilfenil)etil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxipropil)piperazina;

4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-3-(2-hidroxibut-4-inil)piperazina,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-5-(2-hidroxi-2- metilpropil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-3-(2-hidroxietil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3-(2-((2-hidroxietil)amino)etil)-4-(4- fluorobencil)piperazina;

(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,3-dimetilpiperazina;

(2*S*, 5*R*)-1-((4-cloro-3,5-dimetoxifenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(2*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-2,5-dimetilpiperazina,

(2*R*,5*S*)-4- (4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(2- metiltio)etilpiperazina;

(2*R*,5*R*)-4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(benciloxi) metilpiperazina;

(2*R*,5*R*)-1-((4-clorofenoxi) metil)carbonil-2-metil-4-(4-fluorobencil)-5-(((2-hidroxietil)tio) metil)piperazina,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-(*N'*-(etoxicarbonilmetil) ureido)metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-((amino)carboniloxi)metil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-((acetil) metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1-hidroxi-1-(fenil)metil) piperazina,

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1-hidroxibutil)piperazina,

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((dietilamino)metil)piperazina,

(2*R*, 5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) -5-((dimetilamino)metil)piperazina,

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5- (((ciclopropil)amino)metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluoro-bencil)-5- ((morfolin-4-il)metil)piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((piperazin-1- il)metil)piperazina,

(*cis*)-1-((3,4,5-trimetoxifenoxi) metil)carbonil-2,6-dimetil-4-(4-fluorobencil)piperazina;

(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-

2,6- dimetilpiperazina;

1-((fenoxi)metil)carbonil-2-metil-4-(4- fluorobencil)piperazina;

1-((2-(acetilamino)fenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina,

1-((4- clorofenoxi)metil)carbonil-2-(2-hidroxipropil)-4-(4-fluorobencil) piperazina,

1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxibut-3-enil)-4-(4- fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3- trifluorometil-4-(4-fluorobencil)piperazina; y

(*trans*)- 1-((4-cloro-2-((4-(2,5-di(trifluorometil)fenilcarbonil)piperazin-1-il) metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina

De esta subclase de compuestos, un grupo preferido de compuestos es el grupo de compuestos en donde.

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por alquilo, cicloalquilo, hidroxialquilo, hidroxialquenilo, cianoalquilo, alcoxialquilo, monoalquilaminoalquilo, azidoalquilo, monoalquilureidoalquilo, ariloxialquilcarboniloxialquilo, y heterociclilalquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, alquilo, alcoxi, formilo, nitro, ciano, aminoalcoxi, cicloalquilaminoalquilo, hidroxialquilo, (monoalquilamino)aralquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, monoaralquilamino, alquilcarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, (cicloalquialquil)aminoalquilo alcoxicarbonilalquilcarbonilaminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil) (alquil)aminoalquilo, carboxi, alcoxicarbonilo, alquilcarbonilo, (hidroxialcoxi) carbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil)aminocarbonilo, (hidroxialquil)aminocarbonilo, hidroxiamidino, ureido, monoalquilureido, monoarilureido, monoaralquilureido, (monoalquil)(monoaril)ureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoal-

quilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil)ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil) glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil)(alquil) glicinamido, (monoarilaminocarbonil)glicinamido, (monoarilaminocarbonil) (alquil)glicinamido, alaninamido, heterociclilo y heterociclilalquilo.

Los compuestos preferidos dentro de este grupo de compuestos en este grupo de subclase de compuestos se seleccionan del grupo formado por los siguientes compuestos:

1-((3,4,5- trimetoxifenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina,

1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-etilpiperazina;

(2*R*)-4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-2-propilpiperazina;

(2*S*)-4- (4-fluorobencil)-1-((4-clorofenoxi)meil)carbonil-2-propilpiperazina,

4-(4-fluorobencil)-1-(((4-clorofenoxi)metil)carbonil) spiro[ciclopropan-1,2'-piperazina];

1-((4-clorofenoxi)metil) carbonil-2-hidroximetil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-(metoxi)etil) piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2- metilpropil)amino)etil)-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-4-(4-fluorobencil)-5- metilpiperazina;

(2*R*)-1-((4-clorofenoxi)metil) carbonil-3-metil-4-(4-fluorobencil)piperazina,

(2*S*)-1- ((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(hidroximetil)piperazina,

4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-3-(2-hidroxietil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(((metil)ureido) metil)piperazina;

(2*R*,3*R*)-4-(4-fluorobencil)-1- ((4-clorofenoxi)metil)carbonil-2,3-dimetilpiperazina;

(*cis*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetil-4-(4-

fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-2-(2-(((4-clorofenoxi)metil)carbonil)oxi)etil-5- metilpiperazina;

(2*R*,5*R*)-1-((4-clorofenoxi) metil)carbonil-2-metil-4-(4-fluorobencil)-5-((hidroxi)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-2-metil-5-((metoxi)metil)piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4- clorofenoxi) metil)carbonil-2-metil-5-(1-metiletil)piperazina,

(2*R*, 5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-(1-hidroxietil)piperazina;

(2*R*,5*R*)-4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1- hidroxiprop-3-enil)piperazina;

(2*R*,5*S*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((ciano) metil)piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi) metil)carbonil-2-metil-4-(4-fluorobencil)-5-((1,2,4-triazol-2-il)metil) piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)-5-((tetrazolil)metil)piperazina;

(3*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-3,5-dimetilpiperazina, 1-((4-cloro-3-nitrofenoxi) metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- (dietilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-hidroxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-cloro-2-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((etil) (1-metilbutil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

1-((4-cloro-2-aminofenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((4-cloro-3- nitrofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(bencilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-((1-metilbutil)amino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*iso*-propilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diclorofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(4-nitrofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(4-metilfenil)ureido) fenoxi)me-

til)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-bencilureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((ciclopropilmetil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(fenilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- (acetilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((metilamino)(fenil) metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(fenilsulfonil)(metil) aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(acetil)(metil)aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(*N*-metil-*N'*-etilureido)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-((metil)(etil)amino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(dimetilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(2*R*)-1-((4-cloro-2-((4-*t*-butoxicarbonilpiperazin-1-il)me-

til)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil) fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(oxazol-2-ilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(morfolin-4-ilmetil)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-bromo-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-fluoro-3-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

1-((4-cloro-2-metoxicarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-metoxicarbonilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2- aminocarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3-cianofenoxi)metil)carbonil-2,5-dimetil-4- (4-

fluorobencıl)pıperazına;

(*trans*)-1-((4-metıl-2-amınofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((3-formılfenoxı)metıl)carbonıl-2,5-dımetıl- 4-(4-fluorobencil)pıperazına;

(*trans*)-1-((4-metil-2-acetılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((2-metoxıcarbonılfenoxı)metıl)carbonıl-2,5- dımetıl-4-(4-fluorobencıl)piperazına:

(*trans*)-1-((3-nıtrofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-acetil-2-(amınocarbonıl)fenoxı)metil)carbonil-2,5-dimetil-4-(4-fluorobencıl)pıperazina,

(*trans*)-1-((4-nitro-3-metilfenoxı)metıl)carbonıl-2,5-dımetil-4-(4- fluorobencıl)pıperazına;

(*trans*)-1-((5-nıtro-2-metılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-amıno-3-nıtrofenoxı)metıl)carbonıl- 2,5- dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((5-nıtro-2-amınofenoxı)metil)carbonıl-2,5-dimetil-4-(4-fluorobencıl) piperazına;

(*trans*)-1-((2-aminofenoxı)metıl)carbonıl-2, 5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((3- metoxifenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-metoxi-2-acetilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((5- metoxi-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((2-((2-hidroxietil)aminocarbonil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-((2-hidroxietoxi)carbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(2-hidroxietoxi)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-acetil-4,5-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-metoxi-2-(metoxicarbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(*N'*-metilureido)amino)metil)piperazina;

(*trans*)-1-((4-metil-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(*trans*)-1-((3-cloro-5-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metoxi-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(*trans*)-1-((2-(hidroximetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-

fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2- (2-azidoetil)-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ftalimido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(maleimido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4- (bencilcarbonil)piperazin-1-il)metil)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-((2,3,4-trifluorofenil)aminocarbonil)piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((4-((2-fluorofenil)aminocarbonil) piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(2,6-difluorofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(etenilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- (ciclopropilcarbonilamino)fenoxi)metil)carbonil-2 5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- (ciclopentilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((furan-2- ıl)carbonılamıno)fenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(*trans*)-1-((4-cloro-2-(fenılcarbonılamıno) fenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((*N'*-(3-metoxıfenıl)ureıdo) fenoxi)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((*N'*-(metoxıcarbonılmetılcarbonıl)-*N'*-(metıl)glıcınamıdo)fenoxı) metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((*N'*-(2-metoxıcarbonıletil)carbonıl-*N'*-(metıl)glıcınamıdo)fenoxı)metıl)carbonil-2,5-dimetil-4-(4- fluorobencil)pıperazına;

(*trans*)-1-((4-cloro-2-((*N'*-(3-metılbencıl) amınocarbonıl-*N'*-(metıl)glıcinamıdo)fenoxı)metıl)carbonıl-2,5- dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4- cloro-2-((*N'*-(3-trıfluorometil-4-fluorofenıl)carbonıl-*N'*- (metıl)glicınamıdo)fenoxı)metıl)carbonil-2,5-dımetil-4-(4- fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((*N'*-(4-metılbencıl)amınocarbonıl-*N'*-(metıl)glıcınamıdo) fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-clorofenıl)carbonıl-*N'*-(metıl)glıcınamıdo)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)piperazina,

(*trans*)-1-((4-cloro-2-((*N'*-(4-fluorobencil)aminocarbonil-*N'*-(metil)glicinamido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(2-iodofenilcarbonil) glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(2,3-difluorofenilcarbonil)glicinamido)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-((4-fenoxifenil)aminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diflurofenilcarbonil)glicinamido)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((2-iodofenilcarbonil)aminometil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((etoxicarbonilmetilcarbonil) aminometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(3- cloropropil)ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(2-fluoro-6-trifluorome-

tilfenil)ureidometil)fenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((3-fluorofenil) carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'* -(2-(etoxicarbonil)etil)ureidometil)fenoxi)-metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(2*S*)-1-((4-cloro- 2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((2,5-di(trifluorometil)fenil) carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, y

(*trans*)-1-((4-cloro-2-(*N'*-(2-(fenil)ciclopropil)ureidometil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina.

Un grupo más preferido de compuestos en este grupo de subclase de compuestos son los compuestos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por alquilo e hidroxialquilo,

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro,

R^3 es

fenilo sustituido por uno o mas sustituyentes seleccionados entre el grupo formado por halo, alquilo, alcoxi, formilo, nitro, cicloalquilaminoalquilo, hidroxialquilo, amino, alquilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, alquilcarbonilo, aminocarbonilo, monoalquilamino-carbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil) aminocarbonilo, hidroxiamidino, ureido, (haloalquilcarbonil)ureido, ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (amino-carbonil)(alquil)glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, alaninamido, y heterociclilalquilo.

Los compuestos preferidos dentro de este grupo de compuestos más preferido en este grupo de subclase de compuestos se seleccionan del grupo formado por los siguientes compuestos.

(*trans*)-1-((4- cloro-3-nitrofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- (aminocarbonil)fenoxi)metil)carbonil-

2,5-dımetıl-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-1-((4-cloro-2-(amınocarbonıl) fenoxı) metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)piperazına;

(2 *S*,5*R*)-1-((4-bromo-3,5-dımetoxıfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(2*R*,5*S*)-1-((3-hıdroxi-5-metılfenoxi)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına,

(2*S*,5*R*)-1-((4-nıtro-3- formılfenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına,

(2R)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4- fluorobencıl)pıperazına,

4-(4-fluorobencıl)-1-((4-clorofenoxı) metıl)carbonıl-2-(2-hıdroxıetıl)pıperazına,

(*trans*)-4- (4-fluorobencıl)-1-((4-clorofenoxı)metıl)carbonıl-2,5- dımetılpıperazına,

(2*R*,5*S*)-4-(4-fluorobencıl)-1- ((4-clorofenoxı)metıl)carbonıl-2,5-dımetılpıperazına,

(*trans*)-1-((4-cloro-3,5-dımetoxıfenoxı)metıl)carbonıl-2,5-dımetıl- 4-(4-fluorobencıl)pıperazına;

(2*R*,5*S*)-1-((4-cloro- 3,5-dimetoxifenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(2*R*,5*S*)-4-(4-fluorobencıl)-1-((4- clorofenoxı)metil)carbonil-2-(2-hidroxietil)-5-metilpıperazina;

(2*R*,6*R*)-4-(4-fluorobencıl)-1-((4-clorofenoxı)metıl) carbonıl-2,6-dımetılpıperazına;

(*trans*)-1-((4-cloro-2- metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-3- (hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-hidroxietil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4- cloro-2-(ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-aminofenoxi)metil) carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2- (acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina,

(*trans*)-4-(4-fluorobencil)-1-((2-acetilamino- 4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(*trans*)-1-((4-cloro-2-(propilcarbonilamino)fenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-(metoximetilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-(metoxicarbonil)etilcarbonilamino)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-(etoxicarbonil)etilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metilsulfonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(bromometilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(2R)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-metilglicinamido)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(alaninamido)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((aminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((aminocarbonil)(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-etiluredio)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(etilcarbonilamino) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-amino-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal diclorhidrato;

(*trans*)-1-((4-cloro-2-(((etil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(((dietil)amino) metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(((ciclopropil)amino)metil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((dimetil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(((metil)amino)metil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4- cloro-2-((amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-metilpiperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(etilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(metilamino)etil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(1-(metilsulfonil)(metil)aminoetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(2*R*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil) car-

bonıl-2-metıl-4-(4-fluorobencıl)pıperazina,

(2*R*,5 *S*)-1-((4-cloro-2-((pıperazın-1-ıl)metıl)fenoxı)metıl)carbonıl-2,5- dımetil-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((4-*t*-butoxıcarbonılpiperazin-1-ıl)metıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-(ımıdazol-1-ılmetıl)fenoxı)metıl)carbonıl-2,5- dimetil-4-(4-fluorobencıl)pıperazına,

(*trans*)-1-((4-cloro-2-(1-(ımıdazol-1-ıl)etil) fenoxi) metil)carbonıl-2,5-dımetil-4-(4-fluorobencil)piperazına,

(*trans*)-1-((4-cloro-2-(triazol-1-ılmetil)fenoxı)metil)carbonıl-2,5- dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4- cloro-2-(tetrazol-1-ilmetıl)fenoxi)metil)carbonıl-2,5-dımetil-4-(4- fluorobencıl)pıperazina;

(*trans*)-1-((4-cloro-2-((morfolın-4-il)metıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazina,

(2*R*)-1-((4-cloro-2-aminocarbonılfenoxı)metıl)carbonıl-2-metil-4-(4-fluorobencıl) pıperazına;

1-((4-cloro-2-formilfenoxi)metil)carbonil-2-metıl-4-(4-fluorobencil)piperazına;

(2*R*,5*S*)-1-((4-cloro-2-formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(2*R*)-1-((4-cloro-2-formılfenoxı)metıl)carbonil-2-metil-4-(4-fluorobencıl)pıperazına,

(*trans*)-1- ((4-cloro-2-(metılamınocarbonil)fenoxı)metıl)car-

bonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- ((aminocarbonilmetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((2-aminoetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-aminocarbonilfenil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(hidroxiamidino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(triclorometilcarbonil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(metoximetilcarbonil)glicinamido)fenoxi)metil)- carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-(*N'*- (etoxicarbonilaminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina

El grupo más preferido de compuestos dentro de este gru-

po de subclase de compuestos son los compuestos en donde R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y en la posición 2 por aminocarbonilo, ureido, o glicinamido; es decir, los compuestos seleccionados del grupo formado por los siguientes compuestos·

(2*R*,5*S*)-1-((4-cloro-2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(2*R*)-1-((4-cloro-2-(ureido)fenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina,

(*trans*)-1- ((4-cloro-2-(ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(2*R*,5*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(2*R*,5*S*)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

Del subgrupo de compuestos precedente, otra clase preferida de compuestos son los compuestos en donde

R^4 es $-N(R^7)-$;

R^5 es metileno,

R^6 es $-C(O)-$; y

R^7 es

seleccionado del grupo formado por hidrógeno, alquilo, arilo, aralquilo, alquilcarbonilo, alquilcarbonilalquilo,

aralquilcarbonilo, aralquilcarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, y alcoxicarbonilo

De esta clase de compuestos, una subclase preferida de compuestos son los compuestos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, alquilo, cicloalquilo, cicloalquilaminoalquilo, haloalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, alcoxialquilo, aralcoxialquilo, alquiltioalquilo, hidroxialquiltioalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, azidoalquilo, monoalquilureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, hidroxialquilaminoalquilo, ariloxialquilcarboniloxialquilo, aralcoxialquilcarboniloxialquilo, alquilcarbonilalquilo, alcoxicarbonilo, alcoxicarbonilalquilo, y heterociclilalquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo,

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por

hidrógeno, hidroxi, halo, alquilo, alcoxi, hidroxialcoxi, haloalquilo, formilo, nitro, ciano, aminoalcoxi, cicloalquilo, cicloalquilaminoalquilo, aralquilo, hidroxialquilo, (monoalquilamino)aralquilo, alcoxialquilo, amino, monoalquilamino. dialquilamino, monoaralquilamino, alquilcarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, (cicloalquialquil) aminoalquilo, alcoxicarbonilaminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil)(alquil)aminoalquilo, heterociclilaminoalquilo, carboxi, alcoxicarbonilo, alquilcarbonilo, (hidroxialcoxi)carbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil) aminocarbonilo, (hidroxialquil)aminocarbonilo, dialquilaminocarbonilalquilo, hidroxiamidino, ureido, monoalquilureido, monoarilureido, monoaralquilureido, (monoalquil)(mono-

aril)ureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil)ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil)glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil) glicinamido, (monoaralquilaminocarbonil)(alquil)glicinamido, (monoarilaminocarbonil) glicinamido, (monoarilaminocarbonil)(alquil)glicinamido, alaninamido, heterociclilo y heterociclilalquilo

Un grupo preferido de compuestos en este grupo de subclase de compuestos es el grupo en donde

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por alquilo, cicloalquilo, hidroxialquilo, hidroxialquenilo, cianoalquilo, alcoxialquilo, monoalquilaminoalquilo, azidoalquilo, monoalquilureidoalquilo, ariloxialquilcarboniloxialquilo, y heterociclilalquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, alquilo, alcoxi, formilo, nitro, ciano, aminoalcoxi, cicloalquilaminoalquilo, hidroxialquilo, (monoalquilamino)aralquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, monoaralquilamino, alquilcarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, (cicloalquialquil)aminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil) (alquil)aminoalquilo carboxi, alcoxicarbonilo, alquilcarbonilo, (hidroxialcoxi) carbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil)aminocarbonilo, (hidroxialquil)aminocarbonilo, hidroxiamidino, ureido, monoalquilureido, monoarilureido, monoaralquilureido, (monoalquil)(monoaril)ureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoal-

quilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil)ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil)glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil)(alquil) glicinamido, (monoarilaminocarbonil)glicinamido, (monoarilaminocarbonil) (alquil)glicinamido, alaninamido, heterociclilo y heterociclilalquilo

Un grupo más preferido en este grupo de subclase de compuestos son los compuestos en donde·

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por alquilo y hidroxialquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro,

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, alquilo, alcoxi, formilo, nitro, cicloalquilaminoalquilo, hidroxialquilo, amino, alquilcarbonilamino, haloalquilcarbonilamino, al-

coxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, alquilcarbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil) aminocarbonilo, hidroxiamidino, ureido, (haloalquilcarbonil)ureido, ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, alaninamido, y heterociclilalquilo.

Un grupo aún más preferido de compuestos en este grupo de subclase de compuestos son los compuestos en donde R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido. Los compuestos preferidos en este grupo se seleccionan del grupo formado por los siguientes compuestos·

(*trans*)-1-((4-clorofenilamino)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina

1-((4-cloro-2-(aminocarbonil) fenilamino)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; y

1-((4-clorofenilamino)metil)carbonil-2-metil-4-(4- fluorobencil)piperazina;

Del subgrupo de compuestos precedente, otra clase preferida

de compuestos son los compuestos en donde:

R^4 es

$-C(R^8)_2-$;

R^5 es

metileno;

R^6 es

$-C(O)-$; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, alquilo, amino, monoalquilamino, dialquilamino, alquilcarbonilamino, cicloalquilcarbonilamino, cicloalquilalquilcarbonilamino, alcoxicarbonilamino, alquilsulfonilamino, arilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilcarbonilaminoalquilo, cicloalquilcarbonilaminoalquilo, alcoxicarbonilaminoalquilo, heterociclilcarbonilaminoalquilo, arilsulfonilamino, alquilsulfonilaminoalquilo, ureido, monoalquilureido, monohaloalquilureido, ureidoalquilo, monoalquilureidoalquilo, monohaloalquilureidoalquilo, aminoalquilo, monoalquilaminoalquilo, y dialquilaminoalquilo.

Una subclase preferida de compuestos de esta clase de compuestos son los compuestos en donde.

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, alquilo, cicloalquilo, cicloalquilaminoal-

quilo, haloalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, alcoxialquilo, aralcoxialquilo, alquiltioalquilo, hidroxialquiltioalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, azidoalquilo, monoalquilureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, hidroxialquilaminoalquilo, ariloxialquilcarboniloxialquilo, aralcoxialquilcarboniloxialquilo, alquilcarbonilalquilo, alcoxicarbonilo, alcoxicarbonilalquilo, y heterociclilalquilo,

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo,

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, alquilo, alcoxi, hidroxialcoxi, haloalquilo, formilo, nitro, ciano, aminoalcoxi, cicloalquilo, cicloalquilaminoalquilo, aralquilo, hidroxialquilo, (monoalquilamino)aralquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, monoaralquilamino, alquilcarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxi-

carbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil) aminoalquilo, (cicloalquialquil)aminoalquilo, alcoxicarbonilaminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil)(alquil)aminoalquilo, heterociclilaminoalquilo, carboxi, alcoxicarbonilo, alquilcarbonilo, (hidroxialcoxi)carbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil) aminocarbonilo, (hidroxialquil)aminocarbonilo, dialquilaminocarbonilalquilo, hidroxiamidino, ureido, monoalquilureido, monoarilureido, monoaralquilureido, (monoalquil)(monoaril)ureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil)ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil)glicinamido, (alcoxicarbonilami-

noalquilcarbonil)glicinamido, arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil)glicinamido, (monoaralquilaminocarbonil)(alquil)glicinamido, (monoarilaminocarbonil) glicinamido, (monoarilaminocarbonil)(alquil)glicinamido, alaninamido, heterociclilo y heterociclilalquilo

Un grupo preferido de compuestos dentro de esta subclase preferida de compuestos son los compuestos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por alquilo, cicloalquilo, hidroxialquilo, hidroxialquenilo, cianoalquilo, alcoxialquilo, monoalquilaminoalquilo, azidoalquilo, monoalquilureidoalquilo, ariloxialquilcarboniloxialquilo, y heterociclilalquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, alquilo, alcoxi, formilo, nitro, ciano, aminoalcoxi, cicloalquilaminoalquilo, hidroxialquilo, (monoalquilamino)aralquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, monoaralquilamino, alquilcarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, hete-

rociclilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, (cicloalquialquil)aminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil) (alquil)aminoalquilo, carboxi, alcoxicarbonilo, alquilcarbonilo, (hidroxialcoxi) carbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil)aminocarbonilo, (hidroxialquil)aminocarbonilo, hidroxiamidino, ureido, monoalquilureido, monoarilureido, monoaralquilureido, (monoalquil)(monoaril)ureido, (haloalquilcarbonil)ureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil)ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonilglicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil) glicinamido, (alcoxicarbonilaminoalquilcarbonil)glici-namido, arilcarbonilglicinamido, (arilcarbonil)(al-

quil)glicinamido, (monoaralquilaminocarbonil)(alquil)glicinamido, (monoarilaminocarbonil) glicinamido, (monoarilaminocarbonil)(alquil)glicinamido, alaninamido, heterociclilo y heterociclilalquilo

Un grupo más preferido de compuestos dentro de esta subclase de compuestos son los compuestos en donde

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por alquilo y hidroxialquilo,

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, alquilo, alcoxi, formilo, nitro, cicloalquilaminoalquilo, hidroxialquilo, amino, alquilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, alquilcarbonilo, aminocarbonilo, monoalquilaminocarbonilo, monoarilaminocarbonilo, (aminocarbonilalquil)aminocarbonilo, (aminoalquil)aminocarbonilo, hidroxiamidino, ureido, (haloalquilcarbonil)ureido, ureidoalquilo, glicinamido, monoalquilglicinamido, aminocarbonil-

glicinamido, (alcoxialquilcarbonil)glicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, alaninamido, y heterociclilalquilo

, Un grupo aún más preferido de compuestos de este grupo de subclase de compuestos son los compuestos en donde:

R^2 es

4-fluoro;

R^3 es

fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido, y

un R^8

es hidrógeno y el otro R^8 es seleccionado del grupo formado por amino, alquilcarbonilamino, cicloalquilcarbonilamino, cicloalquilalquilcarbonilamino, alcoxicarbonilamino, alquilsulfonilamino, arilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilcarbonilaminoalquilo, cicloalquilcarbonilaminoalquilo, alcoxicarbonilaminoalquilo, heterociclilcarbonilaminoalquilo, arilsulfonilamino, alquilsulfonilaminoalquilo, ureido, monoalquilureido, monohaloalquilureido, ureidoalquilo, monoalquilureidoalquilo, monohaloalquilureidoalquilo, y aminoalquilo.

Los compuestos preferidos de este grupo aún más preferido son los compuestos seleccionados del grupo formado por los siguientes compuestos·

(*trans*)-1-(2-(4-clorofenil)-3-(metilsulfonilamino)propil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(acetilamino)propil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(*trans*)-1-(2-(4-clorofenil)-2- (metilsulfonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(acetilamino) etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-(2-(4-clorofenil)-2-(amino)etil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina,

(*trans*)-1-(2-(4-clorofenil)-2-(ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-(2-(4-clorofenil)-3-(amino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*t*-butoxicarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((etoxicarbonilmetilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-iso-propilureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-(2-cloroetil)ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil) pipera-

zina;

(*trans*)-1-(2-(4-clorofenil)-2-((2-nitrofenil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((4-metoxifenilmetil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2- ((2,4-dinitrofenil)sulfonilamino)etil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(ciclopropilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2- ciclopropiletil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3- ((2-metilpropil)carbonilamino)propil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(cicloppentilcarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*- (*t*-butil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*- (etil)ureido)propil)car-

bonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(3-choropropil) ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-(2-(4-clorofenil)-3-((morfolin-4-il)carbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

De los compuestos de fórmula (Ia), otro grupo preferido de compuestos son los compuestos en donde.

R^3 es

un sistema de anillo heterocíclico sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, alquilo, alquilsufonilo, arilsulfonilo, alcoxi, hidroxialcoxi, haloalquilo, formilo, nitro, ciano, haloalcoxi, alquenilo, alquinilo, arilo, aralquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, alquilcarbonilamino, alcoxicarbonilamino, alquenilcarbonilamino, cicloalquilcarbonilamino, arilcarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbonil)(alquil)amino, (alcoxicarbonil)(alquil)amino, alquilsulfonilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, alquilcarbonilaminoalquilo, arilcarbonilaminoalquilo, (alquilcarbonil)(alquil) aminoalquilo, alcoxicarbonilaminoalquilo,

carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, arilcarbonilo, aralquilcarbonilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, guanidino, ureido, monoalquilureido, ureidoalquilo, monoalquilureidoalquilo, y glicinamido.

De este grupo de compuestos, un subgrupo preferido de compuestos es el grupo de compuestos en donde:

R^4 es -O-, - $N(R^7)$- o -$C(R^8)$-,

R^5 es una cadena alquileno,

R^7 es

seleccionado del grupo formado por hidrógeno, alquilo, arilo, aralquilo, alquilcarbonilo, alquilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, y alcoxicarbonilo; y

cada R^8

se selecciona en forma independiente entre el grupo formado por hidrógeno, alquilo, arilo, aralquilo, hidroxi, alcoxi, hidroxialquilo, alcoxialquilo, amino, monoalquilamino, dialquilamino, alquilcarbonilamino, cicloalquilcarbonilamino, cicloalquilalquilcarbonilamino, alcoxicarbonilamino, alquilsulfonilamino, arilcarbonilamino, alcoxicarbonilalquilcarbonilamino, (alquilcarbo-

nil)(alquil)amino, aralquilcarbonilamino, (aralquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, cicloalquilcarbonilaminoalquilo, alcoxicarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, aralquilcarbonilaminoalquilo, heterociclilcarbonilaminoalquilo, (aralquilcarbonil)(alquil)aminoalquilo, arilsulfonilamino, alquilsulfonilaminoalquilo, ureido, monoalquilureido, monohaloalquilureido, dialquilureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, monohaloalquilureidoalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, carboxialquilo, alcoxicarbonilalquilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, y dialquilaminocarbonilalquilo.

De este subgrupo de compuestos, una clase preferida de compuestos son los compuestos en donde.

R^4 es

-O-;

R^5 es

metileno; y

R^6 es

-C(O)-.

De esta clase de compuestos, una subclase preferida de compuestos son los compuestos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo for-

mado por halo, alquilo, cicloalquilo, cicloalquilaminoalquilo, haloalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, alcoxialquilo, aralcoxialquilo, alquiltioalquilo, hidroxialquiltioalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, azidoalquilo, monoalquilureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, hidroxialquilaminoalquilo, ariloxialquilcarboniloxialquilo, aralcoxialquilcarboniloxialquilo, alquilcarbonilalquilo, alcoxicarbonilo, alcoxicarbonilalquilo, y heterociclilalquilo, y

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo.

Un grupo preferido de compuestos en este grupo preferido de la subclase de compuestos son los compuestos en donde R^3 es seleccionado del grupo formado por azepinilo, acridinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, benzopiranilo, benzopiranonilo, benzofuranilo, benzofuranonilo, benzotienilo, carbazolilo, cinnofinilo, decahidroisoquinolilo, dioxolanilo, furilo, isotiazolilo, quinuclidinilo, imidazolilo, imidazolinilo, imidazolidinilo, isotiazolidinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, indanilo, indolizinilo, isoxazolilo, isoxazolidinilo, morfo-

linilo, naftiridinilo, oxadiazolilo, octahidroindolilo, octahidroisoindolilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxoazepinilo, oxazolilo, oxazolidinilo, piperidinilo, piperazinilo, 4- piperidonilo, fenazinilo, fenotiazinilo, fenoxazinilo, ftalazinilo, pteridinilo, purinilo, pirrolilo, pirrolidinilo, pirazolilo, pirazolidinilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, quinazolinilo, quinoxalinilo, quinolinilo, quinuclidinilo, isoquinolinilo, tiazolilo, tiazolidinilo, tiadiazolilo, triazolilo, tetrazolilo, tetrahidrofurilo, tetrahidropiranilo, tienilo, tiamorfolinilo, tiamorfolinilo sulfóxido, y tiamorfolinilsulfona.

Un grupo más preferido de compuestos en esta subclase preferida de compuestos son los compuestos en donde R^3 es benzopiranilo, benzopiranonilo, benzfuranilo, benzofuranonilo, quinolinilo, indolilo, indolinilo, oxazolilo, imidazolilo, o benzotienilo.

Un compuesto preferido en este grupo más preferido es (*trans*)-1-((benzo[b]piran-2-on-7-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina

Otro aspecto de la invención es un método de tratar la endometrosis en un humano de sexo femenino, y dicho método comprende administrar a un humano de sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de un compuesto de fórmula (Ia) según se ha descri-

to.

Preparación de compuestos de la invención

Los siguientes esquemas de reacción son para la preparación de compuestos de fórmula (Ia) Se entiende que aquellos compuestos de la invención que no se preparan específicamente en los siguientes esquemas de reacción se pueden preparar mediante procesos de síntesis similares sustituyendo de manera apropiada las materias primas y reactivos. También se entiende que en las siguientes descripciones, las combinaciones de los diferentes sustituyentes (*por ejemplo,* sustituyentes R^{1a}, R^2 y R^3) en las fórmulas que se muestran se permiten solamente si dichas combinaciones dan compuestos estables.

Solamente por propósitos de conveniencia, más adelante se ilustra la preparación de compuestos de la invención donde R^3 es solamente fenilo. Se entiende que otros grupos R^3 (que incluyen otro sistemas de anillos carbocíclicos y heterocíclicos) se pueden preparar de manera similar

También se entiende que durante la preparación de los compuestos de la invención, según se describe más adelante, los grupos reactivos adicionales (por ejemplo, grupos hidroxi, amino o carboxi) sobre los compuestos intermediarios que se utilizan en la preparación se pueden proteger según sea necesario mediante el grupo protector apropiado tratando el compuesto intermediario antes de la reacción que

se desea con el precursor del grupo protector apropiado utilizando métodos que conocen aquellos con una experiencia normal en el arte. Luego se pueden eliminar los grupos protectores según se desee utilizando métodos que conocen aquellos con una experiencia normal en el arte, p.ej., por hidrólisis ácida o básica. Dichos grupos protectores y métodos se describen en detalle en Greene, T W y Wuts, P G. M , "Protective Groups in Organic Synthesis", 2a Edición, 1991, John Wiley & Sons Además, las dimetilpiperazinas se pueden preparar en una síntesis asimétrica de acuerdo con el método que se resume en Mickelson, J.W ,Belonga, K.L., Jacobsen, E. J., *Journal of Organic Chemistry* (1995),Vol.60,pp.4177-4123.

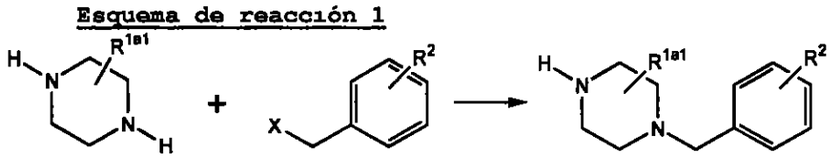
Se debería notar que la única diferencia entre los dos grupos de compuestos que abarca la fórmula (Ia) y la fórmula (Ib) según se describen más adelante es que se requiere la sustitución del anillo piperazina en los compuestos de fórmula (Ia). Por lo tanto, se entiende que, a no ser que se indique de otra manera, los siguientes esquemas de reacción tienen como objeto la preparación de los compuestos de fórmula (Ib) que se pueden utilizar para preparar los compuestos de fórmula (Ia).

A. Preparación de Compuestos de fórmula (C)

Los compuestos de fórmula (C) son intermediarios en la preparación de los compuestos de la invención. Los mismos se preparan de acuerdo con el siguiente esquema de reacción 1

donde R^{1a1} es uno o más sustituyentes R^{1a} que se selecciona independientemente según se describió antes en el resumen de la invención para los compuestos de fórmula (Ia) (excepto que R^{1a1} puede no ser aminoalquilo o monoalquilaminoalquilo a no ser que se proteja de manera apropiada), X es cloro, bromo o yodo; y R^2 es según se describió antes para los compuestos de fórmula (Ia).

Esquema de reacción 1



(A) (B) (C)

Los compuestos de fórmula (A) y fórmula (B) se pueden obtener comercialmente, *p.ej.*, de Aldrich Chemical Co o Sigma Chemical Co., o se pueden preparar de acuerdo con métodos que conocen aquellos con una experiencia normal en el arte.

En general, los compuestos de fórmula (C) se preparan tratando un compuesto de fórmula (A) en un solvente orgánico, como por ejemplo cloruro de metileno, con una cantidad equimolar de un compuesto de fórmula (B) La mezcla de reacción se agita durante entre aproximadamente 10 y 20 horas a temperatura ambiente. Luego se concentra la mezcla de reacción para rendir un residuo que se disuelve en un solvente orgánico. El compuesto de fórmula (C) se aísla desde la so-

lución mediante técnicas de aislación estándar, p.ej., por filtración, concentración y cromatografía rápida en columna.

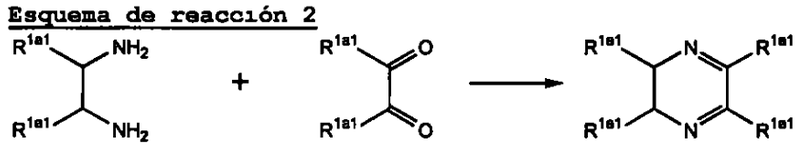
B. Preparación de Compuestos de fórmula (Ga) y Fórmula (Gb)

Los compuestos de fórmula (Ga) y fórmula (Gb) son intermediarios en la preparación de compuestos de la invención. Los mismos se preparan según se ilustra en el siguiente esquema de reacción 2 donde cada R^{1a1} se selecciona independientemente entre el grupo que consiste en alquilo, cicloalquilo, cicloalquilalquilo, cicloalquilaminoalquilo, (cicloalquilalquil)aminoalquilo, haloalquilo, alquenilo, alquinilo, aralquilo, aralquenilo, formilalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, mercaptoalquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, (alcoxi)aralquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, hidroxialquiltioalquilo, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, alcoxicarbonilaminoalquilo, hidroxialquilaminoalquilo, ariloxialquilcarboniloxialquilo, alcoxialquilcarboniloxialquilo, aralcoxialquilcarboniloxialquilo, alquilcarbonilalquilo, carboxialquilo,

alcoxicarbonilalquilo, aralcoxicarbonilalquilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, heterociclilo y heterociclilloalquilo (excepto que R^{1a1} puede no ser aminoalquilo o monoalquilaminoalquilo a no ser que se proteja de manera apropiada):

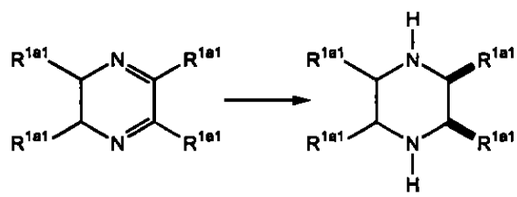
Esquema de reacción 2

1



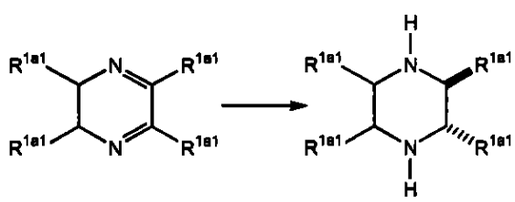
(D) (E) (F)

2a



(F) (Ga)

2b



(F) (Gb)

Los compuestos de fórmula (D) y fórmula (E) se pueden obtener comercialmente, *por ejemplo*, de Aldrich Chemical Co. o Sigma Chemical Co., o se puede hacer utilizando métodos que conocen aquellos con una experiencia normal en el arte.

En general, los compuestos de fórmula (Ga) y fórmula (Gb) se preparan tratando en primer lugar un compuesto de fórmula (D) en un solvente aprótico anhidro, como por ejemplo éter anhidro, con una cantidad equimolar de un compuesto de fórmula (E) en un solvente aprótico anhidro, como por ejemplo éter anhidro, durante un período de tiempo, por ejemplo, durante un período de dos horas. La mezcla de reacción que se obtiene se agita durante entre aproximadamente 2 y aproximadamente 4 horas, preferiblemente durante aproximadamente 3 horas, a temperatura ambiente. El compuesto de fórmula (F) se aísla desde la mezcla de reacción mediante técnicas de aislación estándar, como por ejemplo concentración del producto y purificación por destilación al vacío.

A una solución de un agente reductor fuerte, como por ejemplo hidruro de aluminio y litio, en un solvente aprótico polar anhidro, como por ejemplo tetrahidrofurano, se le agrega el compuesto de fórmula (F) La mezcla resultante se agita a temperatura ambiente durante entre aproximadamente 30 minutos y aproximadamente 2 horas, preferiblemente durante aproximadamente 1 hora. Luego se calienta la mezcla a reflujo para completar la reacción Al completarla, el compuesto de fórmula (Ga) se aísla desde la mezcla de reacción mediante técnicas de aislación estándar, como por ejemplo enfriando con agua y una base suave, seguido de filtración.

Como alternativa, a una solución de fórmula (F) en un

solvente prótico polar, como por ejemplo etanol absoluto, se le agrega a metal alcalino sólido, como p.ej. sodio metálico durante un período de tiempo, como p ej durante un período de 3 horas. La mezcla resultante se calienta a reflujo durante entre aproximadamente 2 y aproximadamente 4 horas, preferiblemente durante aproximadamente 3 horas. El compuesto de fórmula (Gb) se destila desde la mezcla de reacción agregando agua a la mezcla de reacción Luego, el destilado se trata con un ácido acuoso, como p.ej. ácido clorhídrico, para formar la sal del compuesto de fórmula (Gb).

Luego, los compuestos de fórmula (Ga) y fórmula (Gb) se pueden tratar con compuestos de fórmula (B) de manera similar a la que se describió antes en el esquema de reacción 1 para producir compuestos de la invención donde se fija la orientación relativa de los sustituyentes R^{1a}.

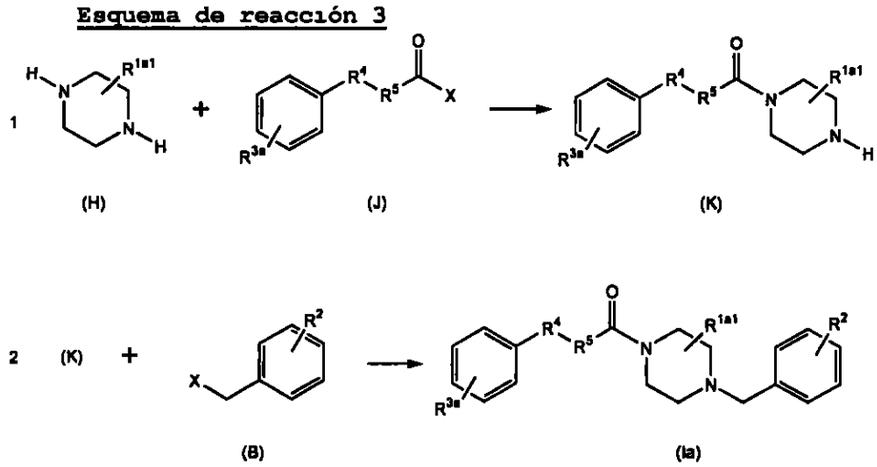
C. Preparación de Compuestos de fórmula (Ia)

Los compuestos de fórmula (Ia) son compuestos de la invención y los mismos se preparan según se ilustra en el siguiente esquema de reacción 3 donde cada X es independientemente cloro o bromo; R^{1a1} es uno o más sustituyentes R^{1a} que se selecciona independientemente según se describió antes en el resumen de la invención para los compuestos de fórmula (Ia) (excepto que R^{1a1} puede no contener una amina primaria o secundaria a no ser que se proteja de manera apropiada); R^2, R^4 y R^5 son según se describe en el resumen de la inven-

ción para los compuestos de fórmula (Ia) (excepto que R^4 y R^5 pueden no contener una amina primaria o secundaria a no ser que se protejan de la manera adecuada); y R^{3a} es uno o más sustituyentes que se seleccionan independientemente entre el grupo que consiste en hidrógeno, hidroxi, hidroxisulfonilo, halo, alquilo, mercapto, mercaptoalquilo, alquiltio, alquilsulfinilo, alquilsufonilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, alcoxi, ariloxi, haloalquilo, formilo, formilalquilo, nitro, nitroso, ciano, aralcoxi, haloalcoxi, cicloalquilo, cicloalquilalquilo, (hidroxi)cicloalquilalquilo, cicloalquilamino, cicloalquilaminoalquilo, (cicloalquilalquil)amino, (cicloalquialquil)aminoalquilo, cianoalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, hidroxialquilo, (hidroxi)aralquilo, hidroxialquiltioalquilo, hidroxialquenilo, hidroxialquinilo, alcoxialquilo, (alcoxi)aralquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, hidroxialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, alcoxicarbonilamino, (alcoxicarbonil)(alquil)amino, alcoxicarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, alquil-

carbonilalquilo, arilcarbonilo, arilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, alcoxialquilcarboniloxialquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, amidino, guanidino, ureido, monoalquilureido, dialquilureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, heterociclilo y heterocicliloalquilo, y R^4 y R^5 son según se describió antes en el resumen de la invención.

Esquema de reacción 3



Los compuestos de fórmula (B), fórmula (H) y fórmula (J) se pueden obtener comercialmente, por ejemplo, de Aldrich Chemical Co o Sigma Chemical Co , o se pueden prepa-

rar de acuerdo con métodos que conocen aquellos con una experiencia normal en el arte.

En general, los compuestos de fórmula (Ia) se preparan mediante el esquema de reacción anterior tratando en primer lugar un compuesto de fórmula (H) en un solvente polar, como por ejemplo metanol, con una cantidad equimolar de un compuesto de fórmula (J) en un solvente polar anhidro, como por ejemplo éter anhidro. La mezcla de reacción que se obtiene se agita a temperatura ambiente durante entre aproximadamente 5 minutos y aproximadamente 24 horas en presencia de una base para neutralizar el ácido, como por ejemplo trietilamina. Luego se aísla el compuesto de fórmula (K) de la mezcla de reacción mediante técnicas de aislación estándar, como p. ej. extracción de la fase orgánica, evaporación de solventes y purificación por cromatografía rápida en columna.

El compuesto de fórmula (K) se trata en un solvente polar aprótico, como p ej tetrahidrofurano, con una cantidad molar en exceso de un compuesto de fórmula (B) en presencia de una base suave, como p.ej. trietilamina y, opcionalmente, una cantidad catalítica de yoduro de sodio. La mezcla resultante se agita a temperatura ambiente durante entre aproximadamente 1 y 5 días, preferiblemente durante aproximadamente 2 días Luego se aísla el compuesto de fórmula (Ia) desde la mezcla de reacción mediante técnicas de aislación estándar como p.ej filtración, concentración de volátiles y pu-

rificación por cromatografía rápida en columna

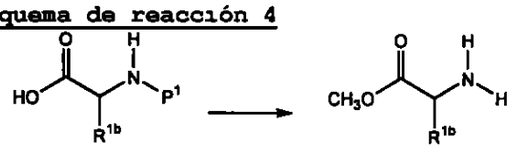
Como alternativa, en este esquema de reacción, en vez de los compuestos de fórmula (H) se pueden utilizar los compuestos de fórmula (Ga) y fórmula (Gb), según se prepararon antes en el esquema de reacción 2, para producir compuestos de la invención donde se fija la orientación relativa de los sustituyentes R^{1a}.

D. Preparación de Compuestos de fórmula (Ia)

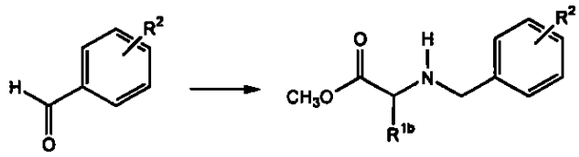
Los compuestos de fórmula (Ia) son compuestos de la invención y los mismos se preparan según se ilustra en el siguiente esquema de reacción 4 donde X es cloro, bromo o un éster activado, P^1 y P^2 son independientemente grupos protectores de nitrógeno, como por ejemplo *t*-butoxicarbonilo (P^1 también puede ser hidrógeno), R^{1a}, R^2, R^4 y R^5 son según se describió antes en el resumen de la invención; R^{1b} es según se describió antes en el resumen de la invención para los compuestos de fórmula (Ic) y (Id); y R^{3a} es uno o más sustituyentes que se seleccionan independientemente entre el grupo que consiste en hidrógeno, hidroxi, hidroxisulfonilo, halo, alquilo, mercapto, mercaptoalquilo, alquiltio, alquilsulfinilo, alquilsufonilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, alcoxi, ariloxi, haloalquilo, formilo, formilalquilo, nitro, nitroso, ciano, aralcoxi, haloalcoxi, cicloalquilo, cicloalquilalquilo, (hidroxi)cicloalquilalquilo, cicloalquilamino, cicloalquilaminoalquilo,

(cicloalquilalquil)amino, (cicloalquialquil)aminoalquilo, cianoalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, hidroxialquilo, (hidroxi)aralquilo, hidroxialquiltioalquilo, hidroxialquenilo, hidroxialquinilo, alcoxialquilo, (alcoxi)aralquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, hidroxialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, alcoxicarbonilamino, (alcoxicarbonil)(alquil)amino, alcoxicarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, alquilcarbonilalquilo, arilcarbonilo, arilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, alcoxialquilcarboniloxialquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, amidino, guanidino, ureido, monoalquilureido, dialquilureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, heterociclilo y heterociclilalquilo

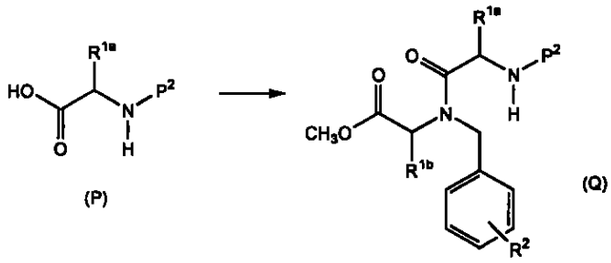
Esquema de reacción 4

1 

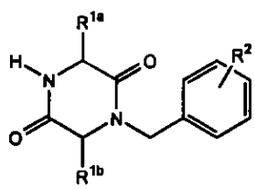
(L) (M)

2 (M) + 

(N) (O)

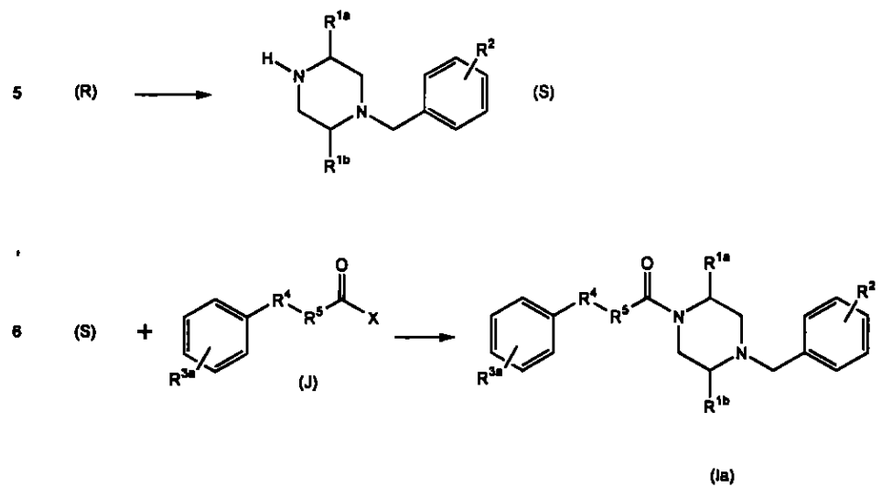
3 (O) + 

(P) (Q)

4 (Q) 

(R)

Esquema de reacción 4 (continuación)



Los compuestos de fórmula (L), fórmula (N), fórmula (P) y fórmula (J) se pueden obtener comercialmente, por ejemplo, de Aldrich Chemical Co o Sigma Chemical Co., o se pueden preparar de acuerdo con métodos que conoce alguien con una experiencia normal en el arte.

Los compuestos de fórmula (L) donde el sustituyente R^{1b} contiene un grupo hidroxi desprotegido se pueden proteger con el grupo protector de oxígeno apropiado antes de la síntesis del compuesto de fórmula (M). La eliminación del grupo protector se puede llevar a cabo según se desee

En general, los compuestos de fórmula (Ia) se preparan en primer lugar esterificando un compuesto de fórmula (L) tratando el compuesto con una cantidad molar en exceso de un alcanol inferior, preferiblemente metanol, en presencia de un ácido, preferiblemente gas clorhídrico, a entre aproxima-

damente 0°C y la temperatura ambiente. Luego se agita la mezcla resultante a entre aproximadamente 0°C y la temperatura de reflujo, preferiblemente a temperatura ambiente, durante entre aproximadamente 4 horas y aproximadamente 18 horas. Luego se concentra la mezcla por eliminación de solventes para producir el compuesto de fórmula (M).

A una solución del compuesto de fórmula (M) en un solvente orgánico, como por ejemplo metanol, a entre aproximadamente 0°C y la temperatura ambiente, se le agrega una cantidad molar en exceso de un compuesto de fórmula (N), y luego se trata con un ácido suave, como por ejemplo ácido acético, y se agita a temperatura ambiente durante entre aproximadamente 2 horas y aproximadamente 4 horas, preferiblemente durante aproximadamente 3 horas, para formar un intermediario imina. La imina se reduce luego *in situ* por tratamiento con un agente reductor, como por ejemplo cianoborohidruro de sodio, para producir un compuesto de fórmula (O), que se aísla desde la mezcla de reacción mediante técnicas de aislación estándar, como por ejemplo filtración y purificación por cromatografía rápida en columna.

A una solución de un compuesto de fórmula (P) en un solvente aprótico polar, como por ejemplo tetrahidrofurano anhidro, se le agrega una base suave para neutralizar el ácido, como por ejemplo *N*-metilmorfolina, seguido de la adición de un reactivo acoplante ácido, como por ejemplo cloro-

formiato de isobutilo. La mezcla resultante se agita a entre aproximadamente 0°C y la temperatura ambiente durante entre aproximadamente 15 minutos y aproximadamente 2 horas, preferiblemente durante aproximadamente 15 minutos a 0°C y luego durante entre aproximadamente una hora a temperatura ambiente, para formar un intermediario activo éster del compuesto de fórmula (P) Luego se trata el intermediario *in situ* con un compuesto de fórmula (O) en solvente aprótico polar anhidro, como por ejemplo tetrahidrofurano anhidro y la mezcla resultante se agita a temperatura ambiente durante entre aproximadamente 10 horas y aproximadamente 24 horas, preferiblemente durante aproximadamente 15 horas El compuesto de fórmula (Q) se aísla desde la mezcla de reacción mediante técnicas de aislación estándar, como p ej. concentración, separación de la fase orgánica y purificación por cromatografía rápida en columna.

Luego se trata el compuesto de fórmula (Q) en un solvente aprótico, como p ej. cloruro de metileno, a aproximadamente 0°C, con un ácido orgánico fuerte, como p.ej. ácido trifluoroacético. Durante un período de entre aproximadamente 2 y aproximadamente 4 horas, preferiblemente durante aproximadamente 2 hs, para eliminar el grupo protector sobre el átomo de nitrógeno,seguido de la ciclización espontánea para formar el compuesto de fórmula (R), que se aísla desde la mezcla de reacción mediante técnicas de aislación están-

dar, como p.ej. neutralización con una base suave, filtración y concentración.

El compuesto de fórmula (R) en un solvente aprótico polar anhidro, como por ejemplo tetrahidrofurano anhidro, a aproximadamente 0°C se trata con un agente reductor fuerte, como por ejemplo hidruro de aluminio y litio Luego se calienta a reflujo la mezcla resultante durante entre aproximadamente 12 horas y aproximadamente 24 horas, preferiblemente durante aproximadamente 15 horas. Luego se enfría la mezcla hasta la temperatura ambiente y la mezcla de reacción se enfría con agua, seguido de una base acuosa, preferiblemente hidróxido de potasio acuoso.La mezcla resultante se deja agitando a temperatura ambiente durante entre aproximadamente 30 minutos y una hora.Luego se aísla el compuesto de fórmula (S) desde la mezcla de reacción por filtración y concentración.

Se agrega el compuesto de fórmula (S) en un solvente aprótico polar, como p.ej. cloruro de metileno, en presencia de una cantidad en exceso de una base para neutralizar el ácido, como p.ej. trietilamina, una cantidad molar levemente en exceso de un compuesto de fórmula (J) en un solvente aprótico polar, como p.ej. cloruro de metileno. La mezcla resultante se agita a temperatura ambiente durante entre aproximadamente 15 minutos y aproximadamente 1 hora, preferiblemente durante aproximadamente 15 minutos. Luego se aís-

la el compuesto de fórmula (Ia) desde la mezcla de reacción mediante técnicas de aislación estándar, como por ejemplo extracción, concentración y cromatografía rápida en columna.

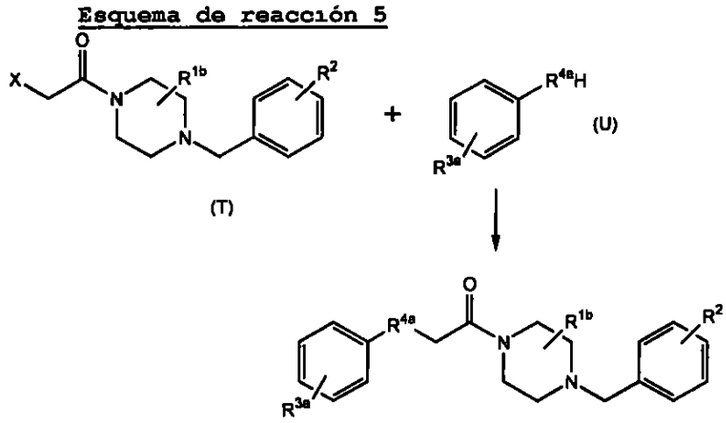
E. Preparación de Compuestos de fórmula (Ib)

Los compuestos de fórmula (Ib) se preparan según se ilustra más adelante en el esquema de reacción 5 donde X es cloro o bromo; R^{1b} es segun se describió antes en el resumen de la invención para R^{1a} de los compuestos de fórmula (Ia) e hidrógeno; y R^2 es según se describió antes en el resumen de la invención para los compuestos de fórmula (Ia); R^{3a} es uno o más sustituyentes que se seleccionan independientemente entre el grupo que consiste en hidrógeno, halo, alquilo, alcoxi, ariloxi, haloalquilo, formilo, nitro, ciano, aralcoxi, haloalcoxi, cicloalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, hidroxialquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, cicloalquilaminoalquilo, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, carboxialquilo, alcoxicarbonilalquilo, ariloxicarbonilalquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, arilsulfonilo, hidroxialcoxi, aminoalcoxi, (monoalquilamino)aralquilo, aminoalquilamino, heterocicliloamino, alquenilcarbonilamino, cicloalquilcarbonilami-

no, arilcarbonilamino, heterociclilocarbonilamino, haloalquilcarbonilamino, alcoxialquilcarbonilamino, alcoxicarbonilalquilcarbonilamino, alquilsulfonilamino, arilcarbonilaminoalquilo, alcoxicarbonilalquilcarbonilaminoalquilo, alquilsulfonilaminoalquilo, (alquilsulfonil)(alquil)aminoalquilo, arilsulfonilaminoalquilo, (arilsulfonil)(alquil)aminoalquilo, heterociclíloaminoalquilo, (hidroxialcoxi)carbonilo, (aminocarbonilalquil)aminocarbonilo, (monoalquilaminocarbonilalquil)aminocarbonilo, (carboxialquil)aminocarbonilo, (alcoxicarbonilalquil)aminocarbonilo, (aminoalquil)aminocarbonilo, (hidroxialquil)aminocarbonilo, dialquilaminocarboniloxialquilo, monoarilureido, monoaralquilureido, monohaloalquilureido, (monoalquil)(monoaril)ureido, diarilureido, (haloalquilcarbonil)ureido, monoarilureidoalquilo, monoaralquilureidoalquilo, monohaloalquilureidoalquilo, (haloalquil)(alquil)ureidoalquilo, (alcoxicarbonilalquil)ureidoalquilo, glicinamido, monoalquilglicinamido, (alcoxialquilcarbonil)glicinamido, aminocarbonilglicinamido, (aminocarbonil)(alquil)glicinamido, (alcoxicarbonilalquilcarbonil)(alquil)glicinamido, (alcoxicarbonilaminoalquilcarbonil)glicinamido, arilcarbonilglicinamido, (arilcarbonil)(alquil)glicinamido, (monoaralquilaminocarbonil)glicinamido, (monoaralquilaminocarbonil)(alquil)glicinamido, (monoarilaminocarbonil)glicinamido, (monoarilaminocarbonil)(alquil)glicinamido, glicinamidoalquilo, alaninamido, monoal-

quilalaninamido, alaninamidoalquilo, heterociclilo y heterociclíloalquilo; y R^{4a} es -O- o $-N(R^{7a})-$ donde R^{7a} es hidrógeno, alquilo, arilo o aralquilo:

Esquema de reacción 5



Los compuestos de fórmula (U) se pueden obtener comercialmente, por ejemplo, de Aldrich Chemical Co. o Sigma Chemical Co., o se pueden preparar de acuerdo con métodos que conocen aquellos con una experiencia normal en el arte. Compuestos de fórmula (T) se puede preparar de acuerdo con los métodos que se describen aquí para los compuestos de fórmula (C) o para los compuestos de fórmula (K), o acilando los compuestos de fórmula (C) según se prepararon aquí utilizando métodos estándar que conocen aquellos con una experiencia normal en el arte.

En general, los compuestos de fórmula (Ib) se preparan mediante el esquema de reacción anterior tratando en primer

lugar un compuesto de fórmula (T) en un solvente aprótico anhidro, como por ejemplo dimetilformamida anhidra, con una cantidad molar levemente en exceso de un compuesto de fórmula (U) en presencia de una base suave, como p.ej carbonato de potasio. La mezcla resultante se agita a aproximadamente 50°C durante entre aproximadamente 10 horas y aproximadamente 24 horas, preferiblemente durante aproximadamente 15 horas. Luego se aísla el compuesto de fórmula (Ib) desde la mezcla de reacción mediante técnicas de aislación estándar, como p.ej. extracción, filtración y precipitación.

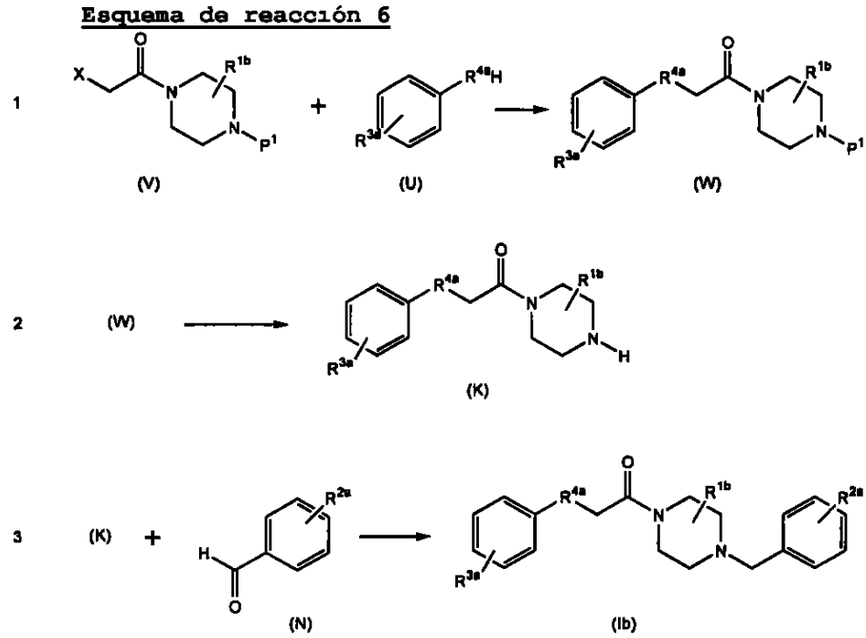
F. Preparación de Compuestos de fórmula (Ib)

Los compuestos de fórmula (Ib) se pueden preparar también según se ilustra en el siguiente esquema de reacción 6 donde X es cloro, bromo o un éster activado; P^1 es un grupo protector de nitrógeno, como por ejemplo *t*-butoxicarbonilo; R^{1b} es según se describió antes en el resumen de la invención para los compuestos de fórmula (Ic) y fórmula (Id); R^{2a} es según se describió antes en el resumen de la invención para R^2 en compuestos de fórmula (Ic) excepto que R^{2a} puede no ser formilo o formilalquilo, R^{3a} es uno o más sustituyentes que se seleccionan independientemente entre el grupo que consiste en hidrógeno, hidroxi, hidroxisulfonilo, halo, alquilo, mercapto, mercaptoalquilo, alquiltio, alquilsulfinilo, alquilsufonilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, alcoxi, ariloxi, haloalquilo, formi-

lo, formilalquilo, nitro, nitroso, ciano, aralcoxi, haloalcoxi, cicloalquilo, cicloalquilalquilo, (hidroxi)cicloalquilalquilo, cicloalquilamino, cicloalquilaminoalquilo, (cicloalquilalquil)amino, (cicloalquialquil)aminoalquilo, cianoalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, hidroxialquilo, (hidroxi)aralquilo, hidroxialquiltioalquilo, hidroxialquenilo, hidroxialquinilo, alcoxialquilo, (alcoxi)aralquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, hidroxialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, alcoxicarbonilamino, (alcoxicarbonil)(alquil)amino, alcoxicarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, alquilcarbonilalquilo, arilcarbonilo, arilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, alcoxialquilcarboniloxialquilo, ami-nocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, amidino, guanidino, ureido,

monoalquilureido, dialquilureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, heterociclilo y heterociclilloalquilo, y R^{4a} es -O- o -N(R^{7a})- donde R^{7a} es hidrógeno, alquilo, arilo o aralquilo·

Esquema de reacción 6



Los compuestos de fórmula (U) y fórmula (N) se pueden obtener comercialmente, por ejemplo, de Aldrich Chemical Co. o Sigma Chemical Co., o se pueden preparar de acuerdo con métodos que conocen aquellos con una experiencia normal en el arte. Los compuestos de fórmula (V) se pueden preparar de acuerdo con el método que se describió antes para los compuestos de fórmula (K) en el esquema de reacción 3.

En general, los compuestos de fórmula (Ib) según se

prepararon en el esquema de reacción anterior 6 se preparan tratando en primer lugar un compuesto de fórmula (U) en un solvente aprótico, como p ej dimetilformamida, a aproximadamente 0°C, con una base fuerte, como por ejemplo hexametildisilazida de potasio, para desprotonar el compuesto. La mezcla resultante se agita durante entre aproximadamente 20 minutos y una hora, preferiblemente durante entre aproximadamente 20 minutos y aproximadamente 0°C Luego se agrega a la mezcla una cantidad equimolar de un compuesto de fórmula (V) en un solvente aprótico, como p.ej. dimetilformamida y la mezcla resultante se agita a temperatura ambiente durante entre aproximadamente 1 y 24 horas, preferiblemente durante aproximadamente 2 horas.Luego se aísla el compuesto de fórmula (W) desde la mezcla de reacción mediante técnicas de aislación estándar,como p.ej. extracción y concentración

Después se elimina el grupo protector P^1 del compuesto de fórmula (W) para formar un compuesto de fórmula (K) mediante procedimientos estándar de desprotección de aminas, por ejemplo tratando el compuesto de fórmula (W) con un ácido fuerte, como por ejemplo ácido trifluoroacético.

A una solución del compuesto de fórmula (K) en un solvente polar, como p ej metanol, a entre aproximadamente 0°C y la temperatura ambiente, se le agrega una cantidad molar en exceso de un compuesto de fórmula (N), y luego se trata con un ácido suave como p.ej. ácido acético, y se agita a

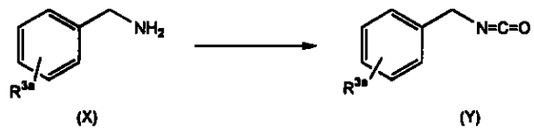
temperatura ambiente durante entre aproximadamente 2 hs y aproximadamente 4 h, preferiblemente durante aproximadamente 3 hs, para formar un intermediario imina. La imina se reduce luego *in situ* por tratamiento con un agente reductor, como p.ej. cianoborohidruro de sodio, para producir un compuesto de fórmula (Ib), que se aísla desde la mezcla de reacción mediante técnicas de aislación estándar, como p.ej filtración y purificación por cromatografía rápida en columna

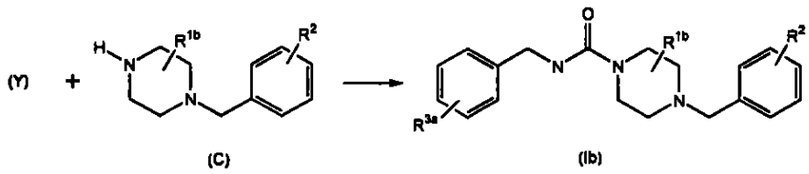
G. Preparación de compuestos de fórmula (Ib)

Los compuestos de fórmula (Ib) también se pueden preparar según se ilustra en el siguiente esquema de reacción 7 donde R^{1b} es según se describió antes en el resumen de la invención para los compuestos de fórmula (Ic) y fórmula (Id); y R^2 es según se describió antes en el resumen de la invención para los compuestos de fórmula (Ib); y R^{3a} es uno o más sustituyentes que se seleccionan independientemente entre el grupo que consiste en hidrógeno, hidroxi, hidroxisulfonilo, halo, alquilo, mercapto, mercaptoalquilo, alquiltio, alquilsulfinilo, alquilsufonilo, alquiltioalquilo, alquilsulfinilalquilo, alquilsulfonilalquilo, alcoxi, ariloxi, haloalquilo, formilo, formilalquilo, nitro, nitroso, ciano, aralcoxi, haloalcoxi, cicloalquilo, cicloalquilalquilo, (hidroxi)cicloalquilalquilo, cicloalquilamino, cicloalquilaminoalquilo, (cicloalquilalquil)amino, (cicloalquilalquil)aminoalquilo, cianoalquilo, alquenilo, alquinilo, ari-

lo, aralquilo, aralquenilo, hidroxialquilo, (hidroxi)aralquilo, hidroxialquiltioalquilo, hidroxialquenilo, hidroxialquinilo, alcoxialquilo, (alcoxi)aralquilo, ariloxialquilo, aralcoxialquilo, amino, monoalquilamino, dialquilamino, monoarilamino, monoaralquilamino, aminoalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, hidroxialquilaminoalquilo, monoarilaminoalquilo, monoaralquilaminoalquilo, alquilcarbonilamino, (alquilcarbonil)(alquil)amino, alquilcarbonilaminoalquilo, (alquilcarbonil)(alquil)aminoalquilo, alcoxicarbonilamino, (alcoxicarbonil)(alquil)amino, alcoxicarbonilaminoalquilo, (alcoxicarbonil)(alquil)aminoalquilo, carboxi, alcoxicarbonilo, aralcoxicarbonilo, alquilcarbonilo, alquilcarbonilalquilo, arilcarbonilo, arilcarbonilalquilo, aralquilcarbonilo, aralquilcarbonilalquilo, carboxialquilo, alcoxicarbonilalquilo, aralcoxicarbonilalquilo, alcoxialquilcarboniloxialquilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, monoarilaminocarbonilo, monoaralquilaminocarbonilo, aminocarbonilalquilo, monoalquilaminocarbonilalquilo, dialquilaminocarbonilalquilo, monoarilaminocarbonilalquilo, monoaralquilaminocarbonilalquilo, amidino, guanidino, ureido, monoalquilureido, dialquilureido, ureidoalquilo, monoalquilureidoalquilo, dialquilureidoalquilo, heterociclilo y heterociclilloalquilo.

Esquema de reacción 7

1 

2 

Los compuestos de fórmula (X) se pueden obtener comercialmente, por ejemplo, de Aldrich Chemical Co. o Sigma Chemical Co., o se pueden preparar de acuerdo con métodos que conocen aquellos con una experiencia normal en el arte. Los compuestos de fórmula (C) se pueden preparar de acuerdo con los métodos que se describen aquí.

En general, los compuestos de fórmula (Ib) preparados según este esquema de reacción se preparan tratando en primer lugar un compuesto de fórmula (X) en un solvente orgánico, como p.ej. tolueno,con fosgeno durante un período de tiempo entre aproximadamente 1 hora y aproximadamente 24 hs, preferiblemente durante aproximadamente 2 horas, a temperatura de reflujo para formar el isocianato de fórmula (Y), que se aísla desde la mezcla de reacción mediante técnicas de aislación estándar,como p.ej. concentración y filtración.

Luego se trata el compuesto de fórmula (Y) en un solvente polar aprótico anhidro, como por ejemplo tetrahidrofurano, con una cantidad equimolar de un compuesto de fórmula

(C). La mezcla resultante se agita a temperatura ambiente durante entre aproximadamente 10 horas y aproximadamente 48 horas, preferiblemente durante aproximadamente 20 horas. Luego se aísla el compuesto de fórmula (Ib) desde la mezcla de reacción mediante técnicas de aislación estándar, como por ejemplo concentración y evaporación de solventes

Además de los anteriores esquemas de reacción 1 a 7, se pueden hacer otros compuestos de la invención utilizando reacciones que conoce alguien con experiencia en el arte. Por ejemplo, un compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada, donde por lo menos un sustituyente R^{1a} o por lo menos un sustituyente R^{1b} se selecciona entre el grupo que consiste en hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, hidroxialquiltioalquilo, e hidroxialquilaminoalquilo, se puede disolver en un solvente polar aprótico, como por ejemplo cloruro de metileno, en presencia de una base suave para neutralizar el ácido y luego se puede tratar con una cantidad molar levemente en exceso de un halogenuro de sulfonilo, como por ejemplo cloruro de sulfonilo, para formar un compuesto intermediario que contiene un grupo saliente sulfonato. El compuesto se puede disolver después en un solvente aprótico anhidro, como por ejemplo dimetilformamida, y tratar, en presencia de una base suave, con el reactivo nucleofílico

apropiado para formar compuestos de fórmula (Ia), o con cualquier materia prima o intermediario de los mismos sustituido de manera apropiada, donde el sustituyente R^{1a} o el sustituyente R^{1b} (dependiendo del reactivo nucleofílico que se utilizan) se puede seleccionar entre el grupo que consiste en heterociclilalquilo, monoalquilaminoalquilo, dialquilaminoalquilo, cicloalquilamino, cianoalquilo, (cicloalquilalquil)aminoalquilo, o hidroxialquiltioalquilo.

Como alternativa, se puede tratar un compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada que contenga un grupo hidroxi, como por ejemplo hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, hidroxialquiltioalquilo, e hidroxialquilaminoalquilo, con un agente oxidante suave, como por ejemplo cloruro de oxalilo, que se disuelve en un solvente orgánico inerte, como por ejemplo cloruro de metileno, al cual se le agrega DMSO durante un período de tiempo a entre aproximadamente -60°C y aproximadamente 0°C, preferiblemente a aproximadamente -50°C. La mezcla de reacción se agita a entre aproximadamente -60°C y aproximadamente 0°C durante entre aproximadamente 15 minutos y aproximadamente una hora, preferiblemente durante aproximadamente 15 minutos, y luego se agrega a la mezcla una base suave, como p.ej. trietilamina. La mezcla se deja calentar gradualmente hasta la temperatura

ambiente, en cuyo punto el compuesto oxidado (*es decir*, el aldehído correspondiente) de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada, se aísla desde la mezcla de reacción mediante técnicas de aislación estándar.

Como alternativa, un compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada, que contenga un aldehído o un grupo cetona, como p.ej formilo, alquilcarbonilo o alquilcarbonilalquilo, se puede tratar con el reactivo organometálico apropiado, como p ej un organomagnesio u organolitio, en condiciones de reacción estándar de síntesis de Grignard para formar los correspondientes compuestos hidroxi-sustituidos.

Como alternativa, un compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada que contenga un grupo hidroxi, como por ejemplo hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, hidroxialquiltioalquilo, e hidroxialquilaminoalquilo, en un solvente polar anhidro, como por ejemplo éter anhidro, en presencia de una base fuerte, como por ejemplo hidruro de sodio, se puede tratar con un halogenuro de alquilo, como por ejemplo yoduro de metilo, a temperatura ambiente, para formar los compuestos alcoxi-sustituidos correspondientes.

Como alternativa, se puede hacer reaccionar un compues-

to de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada, donde por lo menos un sustituyente R^{1a} o por lo menos un sustituyente R^{1b} es formilo o formilalquilo, con una amina primaria o secundaria, en condiciones de aminación reductiva según se describió antes para la preparación de los compuestos de fórmula (O) o los compuestos de fórmula (Ib) según se prepararon en el esquema de reacción 6 para formar los correspondientes compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituidos de manera apropiada, donde el sustituyente R^{1a} o el sustituyente R^{1b} es monoalquilaminoalquilo, dialquilaminoalquilo, monoaralquilaminoalquilo, o hidroxialquilaminoalquilo.

Como alternativa, se puede someter un compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada que contenga un grupo éster, como por ejemplo un grupo alcoxicarbonilo, ariloxicarbonilo o aralcoxicarbonilo, en condiciones estándar de hidrólisis básica, para formar el correspondiente compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada que contenga un grupo ácido, *es decir* un grupo carboxi.

Como alternativa, un compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada, donde R^6 es -C(O)- se puede reducir para

dar el correspondiente compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada, donde R^6 es $-CH_2-$ utilizando métodos que conocen aquellos con una experiencia normal en el arte, p.ej., mediante el método que se describió antes para los compuestos de fórmula (S).

Además, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada, donde R^6 es -C(O)- se pueden convertir en un compuesto de fórmula (Ia), o cualquier materia prima o intermediario del mismo sustituido de manera apropiada, donde R^6 es -C(S)- por tratamiento con reactivo de Lawesson en condiciones estándar que conocen aquellos con una experiencia normal en el arte

Además, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada, que contengan un átomo de azufre no oxidado se puede oxidar con el agente oxidante de azufre apropiado de acuerdo con métodos que conocen aquellos con experiencia en el arte, como por ejemplo utilizando peróxido de hidrógeno, para producir los correspondientes compuestos que contiene un grupo sulfinilo o sulfonilo en vez de los mismos.

Como alternativa, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada que contenga un grupo carboxi se

pueden convertir en compuestos que contengan el grupo amida correspondiente convirtiendo primero el grupo carboxi en un éster activado o anhidruro mixto utilizando, por ejemplo, cloroformiato de isobutilo en presencia de una base suave, como por ejemplo *N*-metilmorfolina, en un solvente aprótico, como por ejemplo THF, y luego tratando el éster con la amina primaria o secundaria sustituida de manera apropiada en un solvente aprótico, como por ejemplo THF.

Como alternativa, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada que contenga un grupo ciano, se pueden convertir en los compuestos que contienen un grupo hidroxiamidino por reacción con la hidroxiamina en un solvente polar, como por ejemplo DMSO. La hidroxiamina se puede preparar *in situ* tratando en primer lugar la sal clorhidrato de la hidroxiamina con una base, como p.ej. trietilamina

Como alternativa, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada que contenga un grupo hidroxi, se pueden convertir en los compuestos que contienen el correspondiente grupo azida tratando el compuesto con trifenilfosfina y un azodicarboxilato de alquilo, por ejemplo azodicarboxilato de dietilo, en un solvente aprótico, como por ejemplo THF, y luego desplazando el oxígeno activado que se formó de esa manera con una azida fuente, como por ejemplo di-

fenilfosforilazida, en un solvente aprótico, como p ej. THF.

Como alternativa, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada, que contengan un grupo $-NH_2$ o un grupo $-R_a-NH_2$ se puede convertir en compuestos que contengan un grupo correspondiente $-R_a-N(H)-C(O)-$ haciendo reaccionar el compuesto con un halogenuro de ácido sustituido de manera apropiada en condiciones estándar de acilación.

Como alternativa, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada, que contengan un grupo halogenuro de ácido (-C(O)-X donde X es halo) o un grupo éster activado se pueden convertir en compuestos que contengan el correspondiente grupo -C(O)-N(H)- haciendo reaccionar el compuesto con una amina primaria o secundaria sustituida de manera apropiada en condiciones estándar de acilación o de formación de uniones amida.

Como alternativa, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada, que contengan un grupo amina primaria o secundaria se pueden convertir en compuestos que contengan el correspondiente grupo aminoalquilo de manera similar a la conversión de fórmula (M) a fórmula (O) en el esquema de reacción 4 En particular, la amina se hace reaccionar con un aldehído sustituido de manera apropiada para

formar el intermediario imina, que se reduce luego por tratamiento con un agente reductor apropiado, como p.ej. cianoborohidruro de sodio

Como alternativa, los compuestos de fórmula (Ia), o cualquier materia prima o intermediario de los mismos sustituido de manera apropiada, que contengan una amina primaria o secundaria se pueden convertir en los compuestos que contienen el correspondiente grupo ureido haciendo reaccionar el compuesto con fosgeno de manera similar al anterior esquema de reacción 7 (en un solvente aprótico) para formar el correspondiente isocianato, que luego se hace reaccionar con la amina primaria o secundaria sustituida de manera apropiada.

Además, todos los compuestos de la invención que existen en forma de base libre o en forma de ácido libre se pueden convertir en sus sales aceptables para uso farmacéutico por tratamiento con el ácido orgánico o inorgánico apropiado, o mediante la base orgánica o inorgánica apropiada Las sales de los compuestos de la invención también se pueden convertir en la forma de base libre o la forma de ácido libre o en otra sal utilizando métodos que conocen aquellos con experiencia en el arte.

Los siguientes preparaciones y ejemplos específicos se dan como una guía para asistir en la práctica de la invención, y no se dan como una limitación del alcance de la invención.

En los siguientes preparación y ejemplos, todos los datos de RMN se refieren a datos de espectros ^1H RMN y se dan en el formato de "(multiplicidad, número de hidrógenos)". El rendimiento de cada una de las reacciones que se describen aquí se expresa como un porcentaje del rendimiento teórico

PREPARACIÓN 1

Compuestos de Fórmula (C)

A. A una solución de 2-metilpiperazina (0,10 g, 1 mmol) en CH_2Cl_2 (2 mL) se agregó bromuro de 4-fluorobencilo (0,125 mL, 1 mmol). La mezcla resultante se agitó a temperatura ambiente. Después de 15 horas, la mezcla se concentró al vacío para dar un sólido. Este sólido se disolvió en CH_2Cl_2 y se lavó en forma consecutiva con agua, solución acuosa de $NaHCO_3$, luego salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró para formar un aceite. La purificación por cromatografía de columna flash dio 0,025 g (12% de rendimiento) de 1-(4-fluorobencil)-3-metilpiperazina, un compuesto de fórmula (C), como un aceite incoloro, RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (m, 2), 3,4 (s, 2), 3,0-2,6 (m, 5), 2,0 (br s, 2), 1,6 (t, 1), 1,0 (d, 3) ppm.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (C):

(2*R*,5*S*)-1-(cloro)acetil-4-(4-fluorobencil)-2,5- dimetil-piperazina-1-(4-fluorobencil)piperazina;

(*trans*)- 1-(4-fluorobencil)-2,5-dimetilpiperazina;

(*cis*)-1-(4- fluorobencil)-2,3-dimetilpiperazina;

(*trans*)-1-(4- fluorobencil)-2,3-dimetilpiperazina; y

(*cis*)-1-(4- fluorobencil)-3,5-dimetilpiperazina

C. en forma similar, se preparan otros compuestos de fórmula (C).

PREPARACIÓN 2

Compuestos de Fórmula (F)

A. A una solución de etilendiamina (13 g, 216 mmol) en éter anhidro (600 mL) se agregó 2,3-butanediona (18,6 g, 216 mmol, en 200 mL éter anhidro) por goteo a lo largo de 2 horas. la mezcla resultante se agitó a temperatura ambiente. Después de 3 horas, la solución límpida se concentró al vacío para dar un aceite de color marrón la purificación por destilación al vacío dio 16,6 g (70% de rendimiento) de 5,6-dimetil-2,3-dihidropirazina, un compuesto de fórmula (F), como un aceite amarillo límpido; b.p 60°C /16 mm Hg, RMN ($CDCl_3$) 3,3 (br s, 4), 2,1 (s, 6) ppm.

B. en forma similar, se preparan otros compuestos de fórmula (F).

PREPARACIÓN 3

Compuestos de fórmula (Ga)

A. A una solución de hidruro de litio y aluminio (0,36 g, 10 mmol) en tetrahidrofurano anhidro (50 mL) se agregó cui-

dadosamente 5,6-dimetil-2,3- dihidropirazina (1,0 g, 9 mmol, en 10 mL de tetrahidrofurano anhidro) La mezcla resultante se agitó a temperatura ambiente durante 1 hora, luego se calentó a reflujo Una vez finalizada la reacción, según la determinación por cromatografía en capa delgada de la mezcla de reacción, la mezcla de reacción se enfrió a temperatura ambiente y se fraguó por adición consecutiva de 0,4 mL de agua, 0,4 mL de solución acuosa de NaOH al 15%, luego 1,2 mL de agua. Después de una agitación breve, la mezcla se filtró a través de un embudo fritado. El filtrado se concentró al vacío para obtener 0. 92 g (90% de rendimiento) de (*cis*)-2,3-dimetilpiperazina, un compuesto de fórmula (Ga), como un aceite amarillo límpido; RMN ($CDCl_3$) 2,7 (m, 4), 2,5 (m, 2), 0,9 (d, 6) ppm.

B. en forma similar, se obtienen otros compuestos de fórmula (Ga).

PREPARACIÓN 4

Compuestos de fórmula (Gb)

A. A una solución de 5,6-dimetil-2, 3-dihidropirazina (2,3 g, 21 mmol) en etanol absoluto (60 mL) se agregó metal de sodio (6,5 g, 280 mmol) en porciones reducidas a lo largo de un período de 3 horas. La mezcla resultante se calentó a reflujo. Después de 3 horas a reflujo, el producto se destiló a partir de la mezcla mientras se agra-

gaban gradualmente 200 mL de agua al recipiente de reacción. El destilado se trató con solución de HCl acuoso 1 N y se concentró al vacío para dar un semisólido. La titulación con acetona dio 0,78 g (20% de rendimiento) de (*trans*)-2,3- dimetilpiperazina, un compuesto de fórmula (Gb), como un sólido anaranjado; RMN (DMSO-d_6) 9,8 (br s, 4), 3,5-3,2 (m, 6), 1,2 (s, 6) ppm

B. en forma similar, se preparan otros compuestos de fórmula (Gb).

PREPARACIÓN 5

Compuestos de Fórmula (K)

A. A una solución de (*cis*)-2,6- dimetilpiperazina (0,115 g, 1,1 mmol) en metanol (35 mL) se agregó cloruro de 4-clorofenoxiacetilo (0,205 g, 1,0 mmol, en solución de 6 mL de éter anhidro) La mezcla resultante se agitó a temperatura ambiente durante 10 minutos y luego se agregó trietilamina (0,10 mL, 0,72 mmol). Después de 30 minutos, la mezcla se concentró al vacío para dar un residuo oleoso. Esté se capturó en éter y se lavó solución saturada acuosa de $NaHCO_3$, luego salmuera. La capa orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar un aceite La purificación por cromatografía de columna flash dio 0,202 g (80% de rendimiento) de (*cis*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetilpiperazina, un compuesto de fórmula (K), como

un aceite límpido e incoloro, RMN ($CDCl_3$) 7,3 (d, 2), 6,9 (d, 2), 4,7 (d, 1), 4,6 (d, 1), 4,4 (d, 1), 3,8 (d, 1), 2,7 (m, 3) , 2,2 (t, 1), 1,1 (m, 6) ppm.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (I):

(3*S*,5*S*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetilpiperazina, y

(3*R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetilpiperazina.

C. en forma similar, se preparan otros compuestos de fórmula (K).

PREPARACIÓN 6

Compuestos de Fórmula (M)

A Una solución de ácido (2*R*)-3-benciloxi-2-(*N* -(t-butoxicarbonil)amino) propanoico (23 g, 78 mmol, $[\alpha]_D$ -4,4° (c = 2, H_2O)) en metanol (250 mL) se enfrió a 0°C y Se burbujeó HCl (g) en la solución hasta la saturación. La mezcla resultante se agitó a temperatura ambiente durante 17 horas y luego se concentró al vacío para dar 17 g (100% de rendimiento) de metiléster de ácido (2*R*)-3-benciloxi-2-aminopropanoico, un compuesto de fórmula (M), como un sólido blanco, RMN (DMSO- d_6) 8,7 (br s, 3), 7,4-7,3 (m, 5), 4,5 (q, 2), 4,4 (br s, 1), 3,8 (s, 2), 3,7 (s, 3) ppm.

B. en forma similar, se preparan otros compuestos de fórmula

(M).

PREPARACIÓN 7

Compuestos de Fórmula (O)

A. Una solución de metiléster de ácido (2*R*)-3-benciloxi-2-aminopropanoico (19 g, 78 mmol) en metanol (350 mL) bajo N_2 se enfrió a 0°C y se agregó ácido acético (2 g, pH 2), seguido por la adición de 4-fluorobenzaldehido, un compuesto de fórmula (N) (12,5 mL, 117 mmol) y cianoborohidruro de sodio (7,3 g, 117 mmol) y tamices moleculares 3 Å (15 g). La mezcla resultante se agitó a temperatura ambiente durante 3 horas, luego se filtró a través de Celite (MeOH). El filtrado se concentró al vacío para dar un líquido límpido Este se capturó en acetato de etilo y se lavó en forma consecutiva con solución acuosa de Na_2CO_3 al 10%, agua, luego salmuera. la fase orgánica luego se secó sobre $MgSO_4$, se filtró, y se concentró al vacío. La purificación por cromatografía de columna en gel de sílice dio 14,7 g (60% de rendimiento) de (metiléster de ácido 2*R*)-3- benciloxi-2-(*N*-(4-fluorobencil)amino)propanoico, un compuesto de fórmula (O), como un aceite límpido e incoloro; RMN ($CDCl_3$) 7,4-7,2 (m, 7), 7,0 (dd, 2), 4,5 (d, 2), 3,9-3,5 (m, 8) ppm, MS (LSIMS) 317.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (O):

metiléster de ácido (2*R*)- 2-(*N*-(4-fluorobencil)amino)propanoico;

metiléster de ácido (2*S*)-2-(*N*-(4-fluorobencil)amino)propanoico;

metiléster de ácido (2*R*)-2-(*N*-(4-fluorobencil)amino)4-metiltiobutanoico,

metiléster de ácido (2*R*)-2-(*N*-(4- fluorobencil)amino)-3-metoxipropanoico,

metiléster de ácido (2 *R*)-2-(*N*-(4-fluorobencil)amino)-3-((2-hidroxietil)tio) propanoico, y

metiléster de ácido (2*R*)-2-(*N*-(4- fluorobencil)amino)-3-metilbutanoico.

C. en forma similar, se preparan los siguientes compuestos de fórmula (O):

metiléster de ácido (2*S*)-2-(*N*-(4-fluorobencil) amino)-4-metiltiobutanoico;

metiléster de ácido (2*S*)-2-(*N*-(4-fluorobencil)amino)-3-metoxipropanoico,

metiléster de ácido (2*S*)-2(*N*-(4-fluorobencil)amino)-3-((2-hidroxietil)tio) propanoico;

(2*S*)-2-(*N*-(4- fluorobencil)amino)-3-metilbutanoico metiléster de ácido,

etiléster de ácido (2 *R*)-2-(*N*-(4-fluorobencil)amino)butanoico,

etiléster de ácido (2*S*)-2-(*N*-(4-fluorobencil)ami-

no)butanoico ;

metiléster de ácido (2*R*)-2-(*N*-(4-clorobencil)amino)butanoico;

metiléster de ácido (2*S*)-2-(*N*-(4-clorobencil)amino) butanoico;

metiléster de ácido (2*R*)-2-(*N*-(4- clorobencil)amino)-4-metiltiobutanoico;

metiléster de ácido (2 *R*)-2-(*N*-(4-clorobencil)amino)-3-metoxipropanoico;

metiléster de ácido (2*R*)-2-(*N*-(4-clorobencil)amino)-3-((2- hidroxietil)tio)propanoico; y

metiléster de ácido (2*R*)-2- (*N*-(4-clorobencil)amino)-3-metilbutanoico

D. en forma similar, se preparan otros compuestos de fórmula (O).

PREPARACIÓN 8

Compuestos de Fórmula (Q)

A. A una solución de *N*-*t*-butoxicarbonil-D-alanina (5,6 g, 30 mmol, $[\alpha]_D$ +23° (c=2, CH_3CO_2H)) en tetrahidrofurano anhidro (150 mL) bajo N_2 a 0°C se agregó *N*-metilmorfolina (3,0 g, 30 mmol), seguido por la adición de isobutilcloroformato (3,7 mL, 30 mmol) , resultando en la formación de un sólido blanco La suspensión resultante se agitó a 0°C durante 15 minutos, y luego a temperatura ambiente durante 1 hora. Una solución de metiléster de ácido

(2*R*)-3-benciloxi-2-(*N*-(4-fluorobencil)- amino)propanoico (7,5 g, 24 mmol, en 50 mL de tetrahidrofurano anhidro) se agregó a la mezcla y la mezcla resultante se agitó a temperatura ambiente. Después de 15 horas, la mezcla se filtró a través de Celite (tetrahidrofurano). El filtrado se concentró al vacío para dar un líquido amarillo, que se disolvió en acetato de etilo, se lavó con agua y luego con salmuera La fase orgánica se separó luego se secó sobre $MgSO_4$, se filtró, y se concentró al vacío La purificación por cromatografía de columna en gel de sílice dio 7,3 g (63% de rendimiento) de metiléster de ácido (2*R*)-3-benciloxi-2-(*N*-(4- fluorobencil)-*N*-(((1*S*)-1-(*t*-butoxi-carbonilamino) etil)carbonil)amino)propanoico,un compuesto de fórmula (Q), como un aceite límpido; RMN ($CDCl_3$) 7,4-7,2 (m, 7), 7,0 (dd, 2), 5,3 (d, 2), 4,9-4,3 (m, 5), 4,1-3,7 (m, 4), 1,6 (s, 9), 1,0 (d, 3) ppm.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (Q):

metiléster de ácido (2*R*)-2-(*N*- (4-fluorobencil)-*N*-(((1*S*)-1-(*t*-butoxicarbonilamino) etil)carbonil)amino)propanoico,

metiléster de ácido (2*S*)-2- (*N*-(4-fluorobencil)-*N*-(((1*S*)-1-(*t*- butoxicarbonilamino)etil)carbonil)amino)propanoico;

metiléster de ácido (2*R*)-2-(*N*-(4-fluorobencil)-*N*-(((1*R*)-1-(*t*-butoxicarbonilamino)etil)carbonil)amino)propanoico;

metiléster de ácido (2*S*)-2-(*N*-(4-fluorobencil)-*N*-(((1*R*)-1-(*t*-butoxicarbonilamino)etil)carbonil)amino)propanoico;

metiléster de ácido (2*R*)-2-(*N*-(4- fluorobencil)-*N*-(((1*S*)-1-(*t*-butoxicarbonilamino)etil)carbonil)amino)-4-metiltiobutanoico,

metiléster de ácido (2*R*)-2-(*N*-(4-fluorobencil)-*N*-(((1*S*)-1-(*t*-butoxicarbonilamino)etil)carbonil)amino)-3-metoxipropanoico;

metiléster de ácido (2*R*)-2-(*N*-(4- fluorobencil)- *N*-(((1*S*)-1-(*t*-butoxicarbonilamino)etil)carbonil)amino)- 3-((2-hidroxietil)tio)propanoico;

metiléster de ácido (2*R*)- 2-(*N*-(4-fluorobencil)-*N*-(((1*S*)-1-(*t*- butoxicarbonilamino)etil)carbonil)amino)-3-metilbutanoico; y

metiléster de ácido (2*R*)-2-(*N*-(4-fluorobencil)-*N*-(((1*S*)-1-(*t*-butoxicarbonilamino)-2-(etoxicarbonil)etil)- carbonil)amino)propanoico.

C. en forma similar, se preparan otros compuestos de fórmula (Q).

PREPARACIÓN 9

Compuestos de Fórmula (R)

A. A una solución de metiléster de ácido (2*R*)-3-benciloxi-2-(*N*-(4-fluorobencil)-*N*-(((1*S*)-1-(*t*-butoxicarbonilamino)etil)carbonil)amino) propanoico (2,0 g, 4 mmol) en CH_2 Cl_2 (25 mL) se enfrió a 0°C y se agregó ácido trifluoroacético (25 mL) por goteo a lo largo de 2 horas. Al finalizar la adición, se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente. Después de 2 horas, la mezcla se concentró al vacío. El aceite amarillo residual se capturó en acetato de etilo y se lavó con solución acuosa de $NaHCO_3$ 1 N. La capa orgánica se separó luego se secó sobre $MgSO_4$, se filtró, y se concentró al vacío para dar 1,2 g (83% de rendimiento) de (2*R*, 5*S*)-1-(4-fluorobencil)-2-(benciloxi)metil-5-metilpiperazina-3,6- diona, un compuesto de fórmula (R), como un aceite límpido; RMN ($CDCl_3$) 7,4-7,2 (m, 7), 7,0 (dd, 2), 5,0 (d, 1), 4,5-4,0 (m, 4), 3,9-3,5 (m, 4), 1,5 (d, 3) ppm, MS (LSIMS) 356.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (R):

(2*R*,5*S*)-1-(4-fluorobencil)-2,5-dimetilpiperazina-3,6- diona;
(2*S*,5*S*)-1-(4-fluorobencil)-2,5-dimetilpiperazina-3,6-diona;
(2*R*,5*R*)-1-(4-fluorobencil)-2,5-dimetilpiperazina-3,6-diona;
(2*S*,5 *R*)-1-(4-fluorobencil)-2,5-dimetilpiperazina-3,6-diona;
(2 *R*,5*S*)-1-(4-fluorobencil)-2-(2-metiltioetil)-5- metilpiperazina-3,6-diona;

(2*R*,5*S*)-1-(4-fluorobencil)-2-(metoximetil)-5-metilpiperazina-3,6-diona;

(2*R*,5*S*)-1-(4-fluorobencil)-2-((2-hidroxietil)tiometil)-5-metilpiperazina-3,6-diona,

(2*R*,5*S*)-1-(4-fluorobencil)-2-(1-metiletil)-5-metilpiperazina-3,6-diona; y

(2*R*,5*S*)-1-(4-fluorobencil)-2-metil-5-(etoxicarbonil)metilpiperazina-3,6-diona.

C. en forma similar, se preparan otros compuestos de fórmula (R):

PREPARACIÓN 10

Compuestos de Fórmula (S)

A. A una suspensión de (2*R*,5*S*)-1-(4- fluorobencil)-2-(hidroxi)metil-5-metilpiperazin-3,6-diona (2,0 g, 7,5 mmol) en tetrahidrofurano anhidro (50 mL) bajo N_2 a 0°C se agregó cuidadosamente hidruro de litio y aluminio (2,2 g, 60 mmol). La suspensión resultante se calentó a reflujo Después de 15 horas, la mezcla se enfrió a temperatura ambiente y cuidadosamente se fraguó con agua (2 mL) , luego solución de KOH acuoso 1N (6 mL). La suspensión resultante se agitó a temperatura ambiente durante 30 minutos, luego se filtró a través de Celite (acetato de etilo) El filtrado se concentró al vacío para dar 1,6 g (90% de rendimiento) de (2*R*,5*S*)-1-(4-fluorobencil)-2- (hidroxi)metil-5- metilpiperazina, un com-

puesto de fórmula (S), como un sólido blanco; RMN ($CDCl_3$) 7,3 (dd, 2), 7,0 (dd, 2), 4,2-4,0 (m, 2), 3,5 (d, 1) 3,0 (m, 2), 2,7 (m, 2), 1,7 (m, 1), 1,0 (d, 3).

B. en forma similar, se prepararon los siguientes compuestos de fórmula (S)·

(2*R*,5*S*)-1-(4- fluorobencil)- 2,5-dimetilpiperazina;

(2*S*,5*S*)-1-(4-fluorobencil)- 2,5-dimetilpiperazina,

(2*R*,5*R*)-1-(4-fluorobencil)- 2,5-dimetilpiperazina;

(2*S*,5*R*)-1-(4-fluorobencil)- 2,5-dimetilpiperazina,

(2*R*,5*S*)-1-(4-fluorobencil)-2-(2-metiltioetilo)-5-metilpiperazina;

(2*R*,5*S*)-1-(4-fluorobencil)-2-(metoximetil)-5-metilpiperazina;

(2*R*,5*S*)-1-(4-fluorobencil)-2-((2-hidroxietil)tiometil)-5-metilpiperazina;

(2*R*,5*S*)-1-(4-fluorobencil)-2-(1-metiletil)-5-metilpiperazina; y

(2*R*,5*S*)-1-(4-fluorobencil)-2-metil-5-(etoxicarbonil)metilpiperazina.

C. en forma similar, se preparan otros compuestos de fórmula (S).

PREPARACIÓN 11

Compuestos de fórmula (W)

A. A una solución de 3,4,5-trimetoxifenol (2,8 g, 15 mmol) en DMF (60 mL) a 0°C se agregó hexametildisilazida de

potasio (32 mL, 16 mmol, 0,5 M solución en tolueno). La mezcla resultante se agitó a 0°C. Después de 20 minutos, se agregó 1-(cloro)acetil- 4-(*t*-butoxicarbonil)piperazina (4,6 g, 15 mmol, en 15 mL de DMF) y la mezcla se agitó a temperatura ambiente Después de 2 horas la mezcla se vertió en agua y se extrajo con acetato de etilo. La capa orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar 6,5 g (100% de rendimiento) de 1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(*t*-butoxicarbonil) piperazina, un compuesto de fórmula (W), como un sólido de color amarillo; RMN ($CDCl_3$) 7,2 (m, 2), 4,6 (s, 2), 3,8 (m, 9), 3,6 (m, 4), 3,4 (m, 4), 1,5 (s, 9) ppm.

B. en forma similar, se preparan los siguientes compuestos de fórmula (W):

1-((4-clorofenil)metil)carbonil-4-(*t*-butoxicarbonil)piperazina;

(3*R*)-1-((4-clorofenil)metil)carbonil-3-metil-4-(*t*- butoxicarbonil)piperazina,

(3*S*)-1-((4-clorofenil)metil) carbonil-3-metil-4-(*t*-butoxicarbonil)piperazina; y

1-((4-clorofenil)metil)carbonil-3-(2-((((4-clorofenoxi)metil)carbonil) oxi)etil)-4-(*t*-butoxicarbonil)piperazina

C. en forma similar, se preparan otros compuestos de fórmula

(W).

PREPARACIÓN 12

Compuestos de fórmula (Y)

A. A una solución de 4-clorobencilamina (0,50 g, 3,5 mmol) en tolueno (15 mL) se agregó fosgeno (7,3 mL, 14 mmol, 1,93 M solución en tolueno) La mezcla resultante se agitó a temperatura ambiente durante 15 minutos,luego se calentó a reflujo Después de 2 horas a reflujo,la mezcla se enfrió a temperatura ambiente y se concentró al vacío para dar 0,70 g (100% de rendimiento) de 4-clorobencilisocianato,un compuesto de fórmula (Y), como un líquido amarillo,RMN ($CDCl_3$) 7,4-7,2 (m, 4), 4,4 (m, 2) ppm.

B. en forma similar, se preparan otros compuestos de fórmula (Y).

EJEMPLO 1

Compuestos de Fórmula (Ia) y Fórmula (Ib)

A. A una solución de (2*R*,5*S*)-1-(4- fluorobencil)-2-(hidroxi)metil-5-metilpiperazina (1,6 g, 6,7 mmol) en CH_2Cl_2 (30 mL) se agregó trietilamina (exceso) y cloruro de 4-clorofenoxiacetilo (1,5 g, 7,4 mmol, por goteo en 10 mL solución de CH_2Cl_2). La mezcla resultante se agitó a temperatura ambiente Después de 20 minutos, el análisis por TLC analítica mostró que el consumo total de material de partida se había producido. La mezcla de volá-

tiles se concentró al vacío y el residuo se capturó en CH_2Cl_2. Éste se lavó con solución saturada acuosa de $NaHCO_3$, luego agua, luego salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró al vacío. La purificación por cromatografía de columna en gel de sílice dio 2,16 g (79% de rendimiento) de (2*R*,5*R*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((hidroxi) metil)piperazina, como una espuma sólida de color amarillo. RMN (DMSO-d_6) 7,7 (br s, 2), 7,3 (m, 4), 6,9 (d, 2), 5,0-4,2 (m, 5), 4,0-3,2 (m, 7), 1. 2 (m, 3) ppm; MS (LSIMS) 406.

B. en forma similar, se prepararon otros compuestos de fórmula (Ia):

1- ((4-clorofenoxi)metil)carbonil-4-(4-fluorobencil)-5-metilpiperazina, sal de ácido trifluoroacético; RMN (DMSO-d_6) 7,6 (m, 2), 7,3 (m, 4), 6,9 (m, 2), 5,0-3,8 (m, 6), 3,5-2,8 (m, 5), 1,4 (m, 3) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-metilpiperazina,

4-bencil-1-((4-clorofenoxi)metil)carbonil-2-fenilpiperazina,

(2*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(1-metiletil)piperazina,

4- (4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(metoximetil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-etilpiperazin-3-ona,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (s, 2), 4,4 (m, 1), 3,7 (m, 1), 3,4 (m, 2), 2,8 (m, 2), 2,0-1,7 (m, 5), 0,9 (m, 3) ppm,

(2*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2- metilpropil)piperazina,

(*trans*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (m, 2), 4,2 (m, 1), 3,6-3,0 (m, 5), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

(2*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-bencilpiperazina,

4-(bencil)-1-((4-clorofenoxi)metil)carbonil-2-fenilpiperazin-3-ona;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxietil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,7 (m, 3) , 3,8-3 2 (m,5), 2,8 (m, 2), 2,2 (m, 2), 2,0 (m, 2), 1,7 (m, 2) ppm,

(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi) metil) carbonil-2,6-dimetilpiperazina; RMN ($DMSO-d_6$) 7,6 (m,

2), 7,3 (m, 4), 6,9 (d, 2), 4,8 (m, 3), 4,4 (m, 3), 3,3 (d, 2), 3,0 (m, 2), 1 4 (m, 6) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-2-(1-metilpropil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metilpiperazina, sal clorhidrato;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-2,5-dimetilpiperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (m, 2), 4,2 (m, 1), 3,6-3,0 (m, 5), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(2*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-(2-metilpropil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(butil)piperazina,

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxietil)-5-metilpiperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (m, 2), 4,6 (m, 3), 3,5 (m, 5), 3,2 (dt, 1), 3,0 (m, 1), 2,8 (dd, 1), 2,2 (m, 2), 1,6 (m, 2), 1,0 (d, 3) ppm,

(2 *S*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2, 5-dimetilpiperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (m, 2), 4,2 (m, 1), 3,6-3,0 (m, 5), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(2*S*,5*S*)-4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina, sal clorhidrato; RMN (DMSO-d_6) 7,6 (m, 2), 7,2 (m, 4), 6,9 (d, 2), 4,8 (m, 2), 4,4 (m, 1), 4,1 (t, 1), 3,9-2,9 (m, 6), 1,5-1. 2 (m, 6) ppm,

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-2,5-dimetilpiperazina sal clorhidrato; RMN (DMSO-d_6) 7,6 (m, 2), 7,2 (m, 4), 6,9 (d, 2), 4,8 (m, 2), 4,4 (m, 1), 4,1 (t, 1), 3,9-2,9 (m, 6), 1,5-1,2 (m, 6) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(1,1- dimetiletil)piperazina;

(2*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-metilpropil)piperazina;

(2 *R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-(((4-clorofenoxi)metil)carbonil)oxi)etil-5-metilpiperazina; RMN ($CDCl_3$) 7,2 (m, 6), 7,0 (m, 2), 6,8 (m, 4), 4,7-4,0 (m, 7), 3,6 (m, 2), 3,4 (m, 1), 3,1 (m, 1), 2,6 (m, 1), 2,3 (m, 2), 2,0 (m, 2), 1. 0 (d, 3) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-3-(metoxicarbonil)metilpiperazina,

(2*S*)- 4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-propilpiperazina;

(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi) metil) car-

bonil-2,3-dimetilpiperazina, sal clorhidrato; RMN (DMSO-d_6) 7,6 (m, 2), 7,2 (m, 4), 6,9 (m, 2), 5,0-4,1 (m, 6), 3. 5-2,9 (m, 4), 1,5-1,2 (m, 6) ppm;

(2*R*)-4-(4-fluorobencil)- 1-((4-clorofenoxi)metil)carbonil-2-bencilpiperazina;

(2 *R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- propilpiperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (m, 2), 4,4 (m, 1), 3,7 (m, 1), 3,4 (m, 2), 3,0 (m, 1), 2. 7 (m,2), 2,0-1,6 (m, 4), 1,2 (m, 2), 0,9 (m, 3) ppm ;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(etoxicarbonil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxietil)piperazina; RMN ($CDCl_3$) 7. 3 (m, 4), 7,0 (t, 2), 6,9 (dd, 2), 4,7 (d, 2), 4,0-3,4 (m, 8), 2,8 (m, 2), 2,3 (m, 1), 1,8 (m, 3) ppm;

4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-3-(hidroximetil)piperazina, RMN ($CDCI_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (t, 2), 4,7 (d, 2), 3,9-3. 2 (m, 7), 2,8-2,2 (m, 4) ppm;

(2*S*)-4-(4-fluorobencil)1- ((4-clorofenoxi)metil)carbonil-2-butilpiperazina;

(2*R*,6*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,6- dimetilpiperazina, sal clorhidrato, RMN ($CDCl_3$) 7. 7 (br s, 2), 7,2 (m, 4), 6,8

(d, 2), 4,6 (s, 2), 4,4 (m, 3), 3,9 (m, 1), 3. 5 (m, 1), 3,2 (m, 1), 2,8 (m, 2), 1,6 (s, 6) ppm;

(2*S*,6*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,6- dimetilpiperazina, sal clorhidrato, RMN ($CDCl_3$) 7. 7 (br s, 2), 7,2 (m, 4), 6,8 (d, 2), 4,6 (s, 2), 4,4 (m, 3), 3,9 (m, 1), 3. 5 (m, 1), 3,2 (m, 1), 2,8 (m, 2), 1,6 (s, 6) ppm;

4-(4-fluorobencil)-1-(((4-clorofenoxi)metil)carbonil)espiro[ciclopropan-1, 2'-piperazina]; RMN ($CDCl_3$) 7,3 (m, 4), 7,0-6,8 (m, 4) , 4,6 (m, 4), 2,8 (m, 2), 2,2-1,6 (m, 4) ppm;

4-(4-fluorobencil)- 1-((4-clorofenoxi)metil)carbonil-2-(trifluorometil)piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-metil-5-(2-metiltio)etilpiperazina, sal clorhidrato;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-((((4-clorofenoxi)metil)carbonil)oxi)metil-piperazina;

(2*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-propilpiperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (s, 2), 3,8 (m, 2), 3,4 (m, 2), 3,2 (m, 2), 2,6 (m, 1), 2,4 (m, 1), 2,2 (m, 1), 1,6-1. 3 (m, 4), 0,9 (m, 3) ppm;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)car-

bonil-2-metil-5-(1-metiletil)piperazina, RMN (DMSO-d_6) 7,6 (m, 2), 7,3 (m, 4), 6,9 (d, 2), 5,0-4,2 (m, 6), 3. 5-3,1 (m, 4), 2,2 (m, 1), 1,2 (d, 3), 0,9 (d, 6) ppm;

(2*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-metilpropil) piperazina,

(2*R*,3*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,3-dimetilpiperazina, sal clorhidrato; RMN (DMSO-d_6) 7,8 (m, 2), 7,3 (m, 4), 6,9 (d, 2), 5,1-3,6 (m, 6), 3,2 (m, 4), 1,5-1,2 (m, 6) ppm;

(3*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-butilpiperazina;

(3*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3- (1-metilpropil)piperazina,

(3*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-metilpropil)piperazina;

(3*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3- butilpiperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(benciloxi)metilpiperazina;RMN ($CDCl_3$) 7,3 (m, 8), 6,8 (m,, 5), 4,5 (m, 6), 3,6 (m, 5), 3,0 (m, 1), 2,7 (dd, 1), 2,3 (d, 1), 1,2 (d, 3) ppm;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxietil) piperazina, sal diclorhidrato;

(2*R*)-4-(4-fluorobencil)- 1-((4-clorofenoxi)metil)carbonil-2-metilpiperazina sal clorhidrato;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-2-metil-5-((4-acetilpiperazin-1-il)metil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-((trifluoroacetilamino)metil)piperazina,

4-(4-fluorobencil)-1- ((4-clorofenoxi)metil)carbonil-3-(etoxicarbonil)metilpiperazina, sal clorhidrato;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina, sal clorhidrato;

(*trans*)-4-(4-fluorobencil)-1-((2-acetilamino-4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina; RMN (DMSO-d_6) 9,5 (br s, 1), 8,1 (br s, 1), 7,7 (m, 2), 7,3 (m, 2), 7,0 (m, 2), 5,0 (m, 2), 4,3 (m, 3), 3,8-2,9 (m, 5), 2,1 (s,3), 1,2 (m, 6) ppm;

4-(4-fluorobencil)-1-((2-((acetilamino)metil)-4-clorofenoxi)metil)carbonil-2,5-metilpiperazina; RMN ($CDCl_3$) 7,3 (m, 3), 7,1 (dd, 1), 7,0 (t, 2), 6,7 (d, 1), 4,7 (m, 2), 4,2-3,4 (m, 10), 3,0 (br s, 1), 2,7 (dd, 1), 2,5 (q, 4), 2,2 (d, 1), 2,0 (m, 4), 1,3 (m, 3), 0,9 (m, 3) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(((*t*- butoxicarbonil)amino)metilpiperazina;

1-((4-cloro-2-(acetilamino)fenoxi)metil)carbonil-2-

metil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6) 10,9 (d, 1), 9,5 (s, 1), 8. 1 (s, 1), 7,6 (d, 2), 7,3 (t, 2), 7,0 (m, 2), 5,0 (q, 2), 4,7 (m, 1), 4,3 (m, 2), 3,9-2. 8 (m, 6), 2,1 (s, 3), 1,4 (d, 1,5), 1,3 (d, 1,5) ppm;

(*trans*)-1-((4-cloro-2-(propilcarbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 9,5 (d, 1), 8,2 (s, 1), 7,8 (t, 2), 7,3 (t, 2), 7,0 (dt, 2), 6,8 (dq, 1), 6,4 (d, 1), 5,2-4,3 (m, 5), 3,9-2,8 (m, 5), 1,8 (d, 3), 1,3 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-(*iso*-propilcarbonilamino)feno-xi)metil)carbonil-2,5-dimetil-4-(4-fluoroben-cil)piperazina; RMN (DMSO-d_6) 9,5 (d, 1), 8. 2 (s, 1), 7,8 (t, 2), 7,3 (t, 2), 7,0 (m, 2), 5,2-4,3 (m, 5), 3,9-2,7 (m, 6) , 1,4-1,1 (m, 12) ppm;

(*trans*)-1-((4-cloro-2-(metoximetilcarbonilami-no)fe-noxi)metil)carbonil-2,5-dimetil-4-(4-fluoroben-cil)piperazina, RMN (DMSO-d_6) 9,3 (s, 1), 8. 2 (s, 1), 7,8 (t, 2), 7,3 (t, 2), 7,1 (m, 2), 5,3-4,2 (m, 5), 4,0 (s, 2), 3. 9-2,8 (m, 8), 1,4-1,2 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-(2-(metoxicarbonil)etilcarbo-nilamino)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 9,5 (s 1), 8,1 (s, 1), 7,8 (t, 2), 7,3 (t, 2), 7,0 (m, 2), 5,2-

4,2 (m, 5) , 3,8 (q, 1), 3,7-3,2 (m, 5), 2,9-2,6 (m, 6), 1,4-1,2 (m, 6) ppm,

(*trans*)-1-((4-cloro-2-(2-(etoxıcarbonıl)etılcarbonılamıno)fenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına; RMN (DMSO-d_6) 9,6 (s. 1), 8,1 (s, 1), 7,8 (t, 2), 7,3 (t, 2), 7,0 (m, 2), 5,2-4,2 (m, 5), 4,0 (q, 2), 3,8 (q, 1), 3,6-3,2 (m, 3), 2. 8- 2,6 (m, 5), 1,4-1,2 (m, 9) ppm,

(*trans*)-1-((4-cloro-2-(metilsulfonilamino)fenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına; RMN (DMSO-d_6) 10,9 (d, 1), 9. 3 (s. 1), 7,7 (d, 2), 7,3-7,2 (m, 4), 7,0 (d, 1), 5,0 (m, 2), 4,7 (m, 1), 4. 4 (m, 3), 3,9 (m, 1), 3,6 (m, 1), 3,4-2,8 (m, 6), 1,4 (d, 1,5), 1,2 (d, 1,5) ppm;

(*trans*)-1-((4-cloro-2-(bromometilcarbonılamıno)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)piperazına; RMN ($CDCl_3$) 10,0 (s 1), 8,4 (s, 1), 7,3 (m, 2), 7,0 (m, 3), 6,9 (m, 1), 4,7 (m, 3), 4,0 (s, 2), 3,8-3,1 (m, 5), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (br d, 3), 1,0 (br s, 3) ppm,

(*trans*)-1-((4-cloro-2-(etılcarbonılamıno)fenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına, RMN ($CDCl_3$) 9,4 (s, 1), 8,5 (s, 1), 7,3 (m, 2), 7,0 (m, 3), 6,8 (d, 1), 4,7 (m, 3), 3,5 (m, 3), 3,1 (m, 2) , 2,7 (dd, 1), 2,5 (q, 1), 2,2 (d, 1),

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1,3 (m, 6), 10 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(acetilaminometil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 8,0 (br s, 1), 7,3 (m, 3), 7,1 (dd, 1), 7,0 (m, 2), 6. 8 (br d, 1), 4,7 (m, 3), 4,4 (d, 1), 3,8-3,0 (m, 6), 2,7 (m, 1), 2,2 (m, 1), 2,0 (s, 3), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(1-(metilsulfonil)(metil)amino-etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluo-robencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (m, 1), 5,6 (q, 1), 4,7 (m, 3), 4,2 (m, 1), 3. 7 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3,1 (m, 1), 2,8 (d, 3), 2,7 (d, 3), 2,3 (br d, 1), 1,6 (d, 3), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(1-(fenilsulfonil)(metil)amino-etil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluoro-bencil)piperazina, RMN ($CDCl_3$) 7,6 (d, 2), 7,3 (m, 6), 6,9 (t, 2), 6,8 (t, 1), 5,6 (q, 1), 4,6 (m, 3), 4,2 (m, 1), 3,6 (m, 2), 3,4 (d, 1), 3,0 (m, 1), 2,6 (m, 4), 2 4 (s, 3), 2,3 (m, 1), 1,3 (m, 6), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(1-(acetil)(metil)aminoetil)feno-xi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)pi-perazina; RMN ($CDCl_3$) 7,2 (m, 4), 7,0 (t, 2), 6,8 (m, 1), 6,0 (m, 1), 5,4 (q, 1), 4,6 (m, 3), 4,2 (m,

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1), 3,5 (q, 2), 3,2 (m, 1), 3,0 (m, 1), 2,6 (m, 4), 2 2 (m, 3), 1,3 (m, 6), 0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-(metilsulfonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (t, 4), 7,2 (br d, 2), 7,0 (t, 2), 5,0 (br s, 1), 4,6 (br s, 1), 4,0 (m, 1), 3,4 (m, 5), 3,0 (m, 2), 2,8 (s, 3), 2,6 (m, 2), 2,2 (br d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

(*trans*)-1-(2-(4-clorofenil)-3-(acetilamino) propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,2 (br d, 2), 7,0 (t, 2), 5,2 (m, 1), 4,6 (br s, 1), 4,2 (m, 1), 3,8 (m, 1), 3,4 (m, 5), 3,0 (m, 1), 2,8 (s, 3), 2. 6 (m, 2), 2,2 (m, 1), 1,2 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-(metilsulfonilamino) etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 5), 7,0 (t, 2), 6,6 (m, 1), 4,9 (q, 1), 4,6 (m, 0,5), 4,2 (br d, 0,5), 3,8 (m, 1), 3,5 (m, 1), 3,4 (m, 1), 3,0 (m, 2), 2. 7 (m, 6), 2,2 (m, 1), 1,2 (m, 3), 0,8 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-(acetilamino)etil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; RMN ($CDCl_3$) 7,8 (m, 1), 7,3 (m, 5), 7,0 (t, 2), 5,3 (m, 1), 4,6 (m, 0,5), 4,1 (t, 0,5), 3,5 (m, 1), 3 4 (m, 1), 3,0 (m, 3), 2,6 (m, 2), 2,2 (m, 1), 2,0 (m, 4),

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1,2 (m, 3), 0,8 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((4-(2,5- di(trifluorometil)fenil-carbonil)piperazin-1-il)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,0 (m, 1), 8,1 (m, 2), 7,9 (t, 1), 7,7 (m, 1), 7,4 (d, 1), 7,3 (m, 2), 7,2 (m, 1), 5,4 (m, 1), 5,0 (m, 2), 4,4 (m, 6), 3,4 (m, 9) , 3,0 (m, 1), 2,8 (m, 1), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((4-(bencilcarbonil)piperazin-1-il)metil) fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,0 (m, 1), 7,9 (t, 2), 7,7. (t, 1), 7,6, (s, 1), 7,5 (d, 1), 7,3 (m, 4), 7,2 (m, 3), 5,4 (m, 1), 5,0 (m, 2), 4,4 (m, 6) , 3,7 (m, 2), 3,4 (m, 6), 3,0 (m, 2), 2,8 (m, 1), 1,4 (dd, 3), 1,2 (dd, 3) ppm,

(*trans*)-1-((4-cloro-2-((4-((2,3,4- trifluorofenil)amino-carbonil)piperazin-1-il)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina: RMN (DMSO-d_6) 11,0 (m, 1), 9,0 (s, 1), 7,9 (t, 2), 7,7. (m, 1), 7,6 (s, 1), 7,5 (m, 1), 7,2 (m, 4), 5,4 (m, 1), 5,0 (m, 2), 4,4 (m, 6), 3,4 (m, 8) , 3,1 (m, 2), 2,8 (m, 1), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((4-((2-fluorofenil)aminocarbo-nil)piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6)

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11,0 (m, 1), 8,6 (s, 1), 7 9 (t, 2), 7,7. (m, 1), 7,6 (s, 1), 7,4 (d, 1), 7,3 (m, 1), 7,3 (t, 2), 7. 2 (m, 3), 5,4 (m, 1), 5,0 (m, 2), 4,3 (m, 6), 3,4 (m, 9), 3,1 (m, 2), 2,8 (m, 1), 1,4 (dd, 3), 1,2 (dd, 3) ppm; .

(*trans*)-1-((4-cloro-2-((*N'*-(2,6-difluorofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 9,6 (br s, 1), 8,6 (s, 1), 7,4 (quin, 1), 7,3 (t, 2), 7,0 (m, 5), 6,9 (d, 1), 4,7 (m, 3), 4,1 (brs, 0,5), 3,8 (br s, 0,5), 3,5 (q, 2), 3,2 (m, 1), 3,0 (m, 1), 2,6 (dd, 1), 2,2 (d, 1), 1,2 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(etenilcarbonilamino) fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,8 (d, 1), 8,6 (s, 1), 7,3 (m, 3), 7,0 (t, 3), 6,9 (d, 1), 6,4 (dd, 2), 5,8 (dd, 1), 4,7 (m, 3), 3,6 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3,0 (m, 1), 2,7 (dd, 1), 2,2 (dd, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

(*trans*)-1-((4-cloro-2-(ciclopropilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,7 (br s, 1), 8,4 (s, 1), 7,3 (m, 2), 7,0 (m, 3), 6,8 (d, 1), 4,7 (m, 3), 3,7 (m, 1), 3,5 (q, 2), 3,1 (m, 2), 2,7 (dd, 1), 2,2 (dd, 1), 1,7 (m, 1), 1,3 (m, 3), 1,0 (m, 5), 0,8 (m, 2)

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ppm;

(*trans*)-1-((4-cloro-2-(ciclopentilcarbonilamino)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,3 (br s, 1), 8,5 (s, 1), 7,3 (t, 2), 7,0 (m, 3), 6,8 (d, 1), 4,7 (m, 3), 3,7 (m, 1), 3,5 (q, 2), 3,1 (m, 2), 2,8 (quin, 1), 2. 7 (dd, 1), 2,2 (dd, 1), 1,9 (m, 3), 1,8 (m, 1), 1,6 (m, 3), 1,3 (m, 3), 0 9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((furan-2-il) carbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6) 10,4 (br s, 1), 9,7 (br d, 1), 8,2 (br s, 1), 7,9 (s, 1), 7,7 (m, 2), 7,3 (m, 3), 7,2 (s, 2), 6,7 (d, 1), 5,3 (br d, 1), 5,0 (m, 2), 4,7 (m, 0,5), 4,5 (m, 0,5), 4,2 (m, 3), 3. 6 (m, 1) , 3,4 (m, 1), 2,8 (m, 1), 1,3 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(fenilcarbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10,0 (s, 1), 8,6 (s, 1), 8,1 (d, 2), 7,5 (m, 3), 7,3 (t, 2), 7,0 (t, 3), 6,8 (d, 1), 4,7 (m, 3), 37 (m, 1), 35 (q, 2), 3,1 (m, 2), 2,7 (dd, 1), 2,2 (dd, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-((etoxicarbonilmetilcarbonilamino) etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 8,6 (m, 1), 7,2 (s, 6),

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7,0 (t, 2), 5,4 (m, 1), 4,2 (q, 2), 3,8 (m, 1), 3,5 (m, 1), 3,4 (m, 3), 3,0 (m, 3), 2,6 (m, 2), 2,2 (m, 2), 1 3 (m, 4,5), 1,1 (m, 1,5), 0,9 (dd, 1,5), 0,7 (dd, 1,5) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-iso-propilureido) etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 6), 7,0 (t, 2), 5,2 (t, 1), 4,6 (m, 0,5), 4,4 (m, 1), 4,2 (t, 0,5), 3,8 (m, 1), 3,5 (m, 1), 3,4 (m, 1), 3,0 (m, 3), 2,6 (m, 1), 2,2 (m, 1), 1,1 (m, 9), 0,9 (dd, 1,5), 0,8 (dd, 1,5) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-(2-cloroetil) ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 6), 7,0 (t, 2), 5,2 (t, 2), 4,6 (m, 0. 5), 4,2 (t, 0,5), 3,5 (m, 6), 3,0 (m, 4), 2,6 (m, 1), 2,2 (m,1), 1,1 (m, 3), 0. 9 (dd, 1,5), 0,8 (dd, 1,5) ppm;

(*trans*)-1-(2-(4- clorofenil)-2- ((2-nitrofenil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina, RMN ($CDCl_3$) 8,1 (d, 1), 7,7 (q, 1), 7,6 (t, 2), 7,3 (m, 6), 7,0 (t, 2), 5,6 (m, 1), 4,6 (m, 0,5), 4,1 (t, 0,5), 3,7-3,2 (m, 3), 3,0 (m, 4), 2,6 (m, 1), 2,2 (m, 1), 1,2 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-((4- metoxifenilmetil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4- fluoro-

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bencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 8), 7,0 (t, 2), 6,9 (d, 2), 5,3 (m, 1), 4,6 (m, 0,5), 4,1 (t, 0,5), 3,8 (s, 3), 3. 5 (m, 3), 3,4-2,8 (m, 6), 2,6 (m, 1), 2,2 (m, 1), 1,2 (m, 3), 0,8 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-((2,4-dinitrofenil) sulfonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 8,6 (s, 1), 8,2 (d, 1), 7,8 (m, 1), 7,3 (m, 4), 7,0 (t, 2), 6,9 (t, 2), 5,0 (m, 1), 4,6 (m, 0,5), 4,1 (m, 0,5), 3. 5 (m, 1), 3,4 (m, 1), 3,0 (m, 5), 2,6 (m, 1), 2,2 (m, 1), 1,1 (m, 3), 0,8 (m, 3) ppm,

(*trans*)-1-(2-(4-clorofenil)-2- (ciclopropilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 6), 7,0 (t, 2), 5,2 (m, 1), 4,6 (m, 0,5), 4,2 (m, 0,5), 3,5 (m, 2), 3,4 (m, 1), 3,0 (m, 3), 26 (m, 2), 2,2 (m, 1), 1,5 (m, 1), 1,2 (m, 3), 0,9 (m, 3,5), 0,7 (m, 3,5) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-((2-ciclopropiletil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 6), 7,0 (t, 2), 5,4 (m, 1), 4,6 (m 0,5), 4,2 (m, 0,5), 3,6 (m, 2), 3,4 (m, 1), 3 0 (m, 4), 2,6 (m, 1), 2,2 (m, 2), 1,6 (m, 10), 1,2 (m, 3), 1,1 (m, 2), 0. 8 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-((2-metilpropil)carbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)

piperazina;; RMN ($CDCl_3$) 7,3 (d, 4), 7,2 (d, 2), 7,0 (t, 2), 6,0 (br s, 1), 4,6 (m, 0,5), 4,2 (m, 0,5), 3,6 (m, 2), 3,4 (m, 3), 3. 0 (m, 2), 2,6 (m, 3), 2,2 (d, 1), 2,0 (m, 4), 1,2 (m, 3), 0,9 (m, 9) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-(cicloppentilcarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCI_3$) 7,3 (d, 4), 7,2 (d, 2), 7,0 (t, 2), 6,0 (br s, 1), 4,6 (m, 0,5), 4,2 (m, 0,5), 3,6 (m, 2), 3,4 (m, 3), 3,0 (m, 2), 2,6 (m, 3), 2,4 (m, 1), 2,2 (d, 1), 1,6 (m, 8), 1,1. (m, 4), 0,9 (m, 4) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(*t*- butil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (d, 4), 7,2 (d, 2), 7,0 (t, 2), 4,6 (m, 1,5), 4,2 (m, 0,5), 3,6 (m, 2), 3,4 (m, 4), 3,2 (m, 1), 3,0 (m, 1), 2. 6 (m, 2), 2,2 (d, 1), 1,3 (s, 9), 1,2 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(etil)ureido)propil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (d, 4), 7,2 (d, 2), 7,0 (t, 2), 5,1 (m, 1), 4,9 (m, 1), 4,6 (m, 0,5), 4,2 (m, 0,5), 3,6 (m, 2), 3,4 (m, 4), 3,2 (m, 3), 3,0 (m, 1) , 2,6 (m, 3), 2,2 (m, 1), 1,1 (m, 6), 0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(3-choropropil)ureido) propil)carbonil-2,5-dimetil-4-(4-fluorobencil)pipe-

razina; RMN ($CDCl_3$) 7,3 (d, 4), 7,2 (d, 2), 7,0 (t, 2), 5,6 (br s, 1), 5,9 (s, 1), 4,6 (m, 0,5), 4,2 (m, 0,5), 3,6 (m, 5), 3,4 (m, 5), 3,2 (m, 1), 3 0 (m, 1), 2,6 (m, 3), 2,2 (d, 1), 2,0 (t, 2), 1,2 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-((morfolin-4-il) carbonil-amino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina, RMN ($CDCl_3$) 7,3 (d, 4), 7,2 (d, 2), 7,0. (t, 2), 5,8 (br d, 1), 4,6 (m, 0,5), 4,2 (m, 0,5), 3,6 (m, 6), 3,4 (m, 4), 3,3 (t, 4), 3,0 (m, 2) , 2,6 (m, 3), 2,2 (m, 1), 1,2 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((*N'*-(metoxicarbonilmetilcarbo-nil)-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,6 (br s, 1), 8 4 (d, 1), 7,3 (dd, 2), 7,0 (t, 3), 6,8 (d, 1), 4,7 (m, 3), 4,3 (s, 2), 3. 8 (s, 3), 3,6 (m, 4), 3,5 (m, 2), 3,1 (m, 4), 2,7 (dd, 1), 2,2 (d, 1), 1. 3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((*N'*-(2-metoxicarboniletil)carbo-nil-*N'*-(metil)glicinamido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,6 (br s, 1), 8,4 (d, 1), 7,3 (dd, 2), 7,0 (t, 3), 6. 8 (d, 1), 4,7 (m, 3), 4,3 (s, 3), 3,8 (s, 3), 3,6 (q, 2), 3,2 (s, 3), 3,1 (s, 2) , 2,7 (m, 5), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((*N'*-(3-metilbencil) aminocarbonil-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9.6 (br s, 1), 8,4 (d, 1), 7,3 (dd, 2), 7,2 (t, 1), 7,0 (m, 6), 6,8 (d, 1), 5. 4 (t, 1), 4,6 (m, 3), 4,4 (d, 2), 4,3 (s, 2), 3,8 (m, 1), 3,5 (q, 2), 3. 1 (m, 5), 2,6 (m, 1), 2,3 (s, 3), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((*N'*-(3- trifluorometil-4- fluorofenil)carbonil-*N'*-(metil)glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,8 (br s, 1), 8,4 (d, 1), 8,1 (br s, 1), 7,6 (m, 2), 7,3 (dd, 2), 7,0 (m, 4), 6,8 (d, 1), 4,7 (m, 3), 4,3 (t, 2), 3,7 (m, 1), 3,6 (q, 2), 3,2 (s, 3), 3,1 (m, 2), 2,7 (m, 1), 2,2 (d, 1), 1,3 (m, 3), 0. 9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((*N'*-(4- metilbencil)aminocarbonil-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 9,6 (br s, 1), 8,4 (d, 1), 7,3 (m, 2), 7,2 (d, 2), 7,1 (d, 2), 7,0 (m, 3), 6,8 (d, 1), 5,4 (t, 1), 4,7 (m, 3),4,4 (d, 2), 4,2 (d, 2), 3,8 (m, 1), 3,6 (q, 2), 3,1 (m, 5), 2,7 (m, 1), 2,3 (s, 3), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

(*trans*)-1-((4-cloro-2-((*N'*-(3-clorofenil)carbonil-*N'*-

(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,9 (br s, 1), 8,4 (d, 1), 7,5 (s, 1), 7,3 (m, 5), 7,0 (t, 3), 6,8 (d, 1), 4,7 (m, 3), 4,4 (br s, 2), 4,1 (m, 1), 3,6 (m, 1), 3,5 (q, 2), 3,2 (m, 3), 3,0 (m, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((*N'* -(4-fluorobencil)aminocarbonil-*N'*-(metil)glicinamido)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,7 (br s, 1), 8,4 (s, 1), 7,3 (m, 4), 7,0 (m, 5), 6,8 (d, 1), 5,5 (t, 1), 4,7 (m, 2) 4,4 (d, 2), 4,2 (m, 2), 3,6 (m, 1), 3,5 (q, 2), 3,1 (m, 5), 2,7 (m, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-(metoximetilcarbonil) glicinamido)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 10,1 (br s, 1), 8,4 (d, 1), 7. 3 (t, 3), 7,0 (t, 3), 6,8 (d, 1), 4,7 (m, 3), 4,2 (d, 2), 4,0 (s, 2), 3,6 (m, 1), 3,5 (q, 2), 3,4 (s, 3), 3,1 (m, 2), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

(*trans*)-1-((4-cloro-2-(*N'*- (etoxicarbonilaminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9. 9 (br s, 1), 8,4 (m, 2), 7,3 (m, 3), 7,0 (m, 3), 6,8 (d,

1), 4,7 (m, 3), 4. 4 (m, 6), 3,6 (m, 1), 3,5 (q, 2), 3,1 (m, 2), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 6), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-(2-iodofenilcarbonil)glicinamido)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10. 4 (br s, 1), 8,4 (d, 1), 7,9 (d, 1), 7,5 (d, 1), 7,4 (t, 1), 7,3 (m, 2), 7,1 (t, 1), 7,0 (t, 3), 6,8 (m, 2), 4. 7 (m, 3), 4,4 (d, 2), 3,6 (m, 1), 3,5 (q, 2), 3,1 (m, 2), 2,7 (dd, 1), 2. 2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-(2,3-difluorofenilcarbonil)glicinamido)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 10,3 (br s, 1), 8,4 (d, 1), 7,8 (t, 1), 7,5 (quin, 1), 7,3 (m, 3), 7,2 (m, 1), 7,0 (t, 3), 6,8 (d, 1), 4,7 (m, 3), 4,4 (d, 2), 36 (m, 1), 3,5 (q, 2), 3,1 (m, 2), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0. 9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-((4- fenoxifenil)aminocarbonil)glicinamido)fenoxi)-metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9. 9 (br s, 1), 8,3 (br s, 1), 7,3 (m, 6), 7,0 (t, 6), 6,8 (m, 3), 6,5 (m, 1) , 4,7 (m, 3), 4,4 (m, 2), 3,6 (m, 1), 3,5 (q, 2), 3,1 (m, 2), 2,7 (dd, 1), 2,2 (d,

1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4- cloro-2-(*N'*-(2,4-diflurofenilcarbonil)glicinamido)fenoxi)metil) -carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 10,3 (br s, 1), 8,4 (d, 1), 8,1 (q, 1), 7,5 (m, 1), 7 3 (m, 2), 7,0 (t, 3), 6,8 (m, 3), 4,7 (m, 3), 4,4 (d, 2), 3,6 (m, 1), 3,5 (q, 2), 3,1 (m, 2), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((2-iodofenilcarbonil)aminometil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 8,0 (m, 1), 7,8 (d, 1), 7,3 (m, 5), 7,2 (dd, 1), 7,0 (m, 3), 6,8 (d, 1), 4,8 (m, 3), 4,6 (d, 2), 4,4 (m, 0,5), 3,9 (m, 0,5), 3,5 (q, 2) , 3,1 (m, 2), 2,6 (m, 1), 2,2 (m, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2- ((etoxicarbonilmetilcarbonil)aminometil)fenoxi)-metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 8. 4 (br s, 1), 7,3 (m, 3), 7,2 (dd, 1), 7,0 (m, 2), 6,8 (d, 1), 4,8 (m, 3), 4. 5 (d, 2), 4,2 (m, 3), 3,6 (m, 1), 3,5 (q, 2), 3,3 (s, 2), 3,1 (m, 1), 2. 6 (m, 1), 2,2 (d, 1), 1,3 (m, 6), 0,9 (m, 3) ppm,

(*trans*)- 1-((4-cloro-2-(*N'*-(3-cloropropil)ureidometil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,3 (m, 3), 7,2

(dd, 1), 7,0 (m, 2), 6,8 (d, 1), 4,8 (m, 4), 4,4 (d, 2), 4,2 (m, 1), 3,6 (m, 5), 3,3 (m, 3), 3,1 (m, 1), 2;6 (m, 1), 2. 2 (d, 1), 1,9 (quin, 2), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-(2-fluoro-6- trifluoro-metilfenil)ureidometil)fenoxi)-metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 8,2 (m, 1), 7,3 (m, 6), 7,2 (dd, 1), 7,0 (t, 2), 6,8 (d, 1), 4,8 (m, 3), 4,4 (d, 2), 3,8 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3,1 (m, 1), 2,6,(m, 1), 2,2 (m, 1), 1 3 (m, 3), 0,9 (m, 3) ppm,

(*trans*)-1-((4-cloro-2-((3-fluorofenil) carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; RMN ($CDCl_3$) 8,6 (m, 1), 7,8 (t, 2), 7,3 (m, 4), 7,2 (dd, 1), 7,1 (dt, 1), 7,0 (t, 2), 6,8 (d, 1), 4,8 (m, 3), 4,6 (d, 2), 3,8 (m, 1), 3,5 (q, 2), 31 (m, 2), 2,6 (m, 1), 2,2 (d, 1), 1 3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2- (*N'*-(2-(etoxicarbonil)etil)ureidometil)fenoxi)-metil)carbonil- 2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,3 (m, 3), 7,2 (dd, 1), 7,0 (t, 2), 6,9 (m, 1), 6,8 (d, 1), 5,1 (m, 1), 4,8 (m, 3), 4,4 (d, 2), 4,1 (q, 2), 3,6 (m, 2), 3,4 (m, 3), 3,2 (m, 1), 3 1 (m, 2), 2,7 (m, 1), 2,5 (t, 2), 2,2 (d, 1), 1,3 (m, 6), 0,9 (m, 3) ppm,

(*trans*)-1-((4-cloro-2-((2,5-di(trifluorometil)fenil) carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina, RMN ($CDCl_3$) 8,9 (m, 1), 7,8 (m, 2), 7,2 (s, 1), 7,3 (m, 3), 7,2 (dd, 1), 7,0 (t, 2), 6,8 (d, 1), 4,8 (m, 3), 4,6 (d, 2), 4,4 (m, 0,5), 3,9 (m, 0,5), 3,5 (q, 2), 3,1 (m, 2), 2 6 (m, 1), 2,2 (m, 1), 1,3 (m, 3), 0,9 (m, 3) ppm; y

(*trans*)-1-((4-cloro-2-(*N'*-(2-(fenil)ciclopropil)ureidometil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 8), 7,0 (m, 3), 6,8 (d, 1), 4,9 (s, 1) , 4,6 (d, 2), 4,4 (m, 2), 3,8 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3,0 (m, 1), 2,7 (m, 2), 2. 2 (m, 1), 2,0 (m, 1), 1,3 (m, 5), 0,9 (m, 3) ppm.

C. en forma similar, se prepararon los siguientes compuestos de fórmula (lb):

1-(2-(4-clorofenil)etenil)carbonil-4-(4-fluorobencil)piperazina,

1-(2-(4-clorofenil)etil)carbonil-4-(4-fluorobencil)piperazina,

1-(1-(*t*-butoxicarbonil)amino-2-(4-clorofenil)etil)carbonil-4-(bencil) piperazina;

1-(3-(*t*-butoxicarbonil)amino-2-(4- clorofenil)propil)carbonil-4-(4-fluorobencil)piperazina; RMN (CDCl

$_3$) 7,2 (m, 8), 4,8 (m, 1), 3,6-3,3 (m, 8), 2,6 (m, 2), 2 3 (m, 3), 2,1 (m, 1), 1,4 (s, 9) ppm;

1-(2-(3,4,5-trimetoxifenil)etenil)carbonil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,6 (d, 1), 7,3 (m, 4), 6,7 (m, 3), 3,9-3,6 (m, 13), 3. 5 (s, 2), 2,5 (m, 4) ppm;

1-(1-(3,4-dimetoxifenil)-2-(4-clorofenil)etenil)carbonil-4-(4-clorobencil)piperazina,

1-(2-(3,4,5-trimetoxifenil)etil)carbonil-4-(4-clorobencil)piperazina;

1-(((acetil)amino)(4-clorofenil)metil)carbonil-4-(4-fluorobencil)piperazina, sal clorhidrato.

EJEMPLO 2

Compuestos de Fórmula (Ia)

A. A una solución de (2*R*,5*S*)-1-(cloro)acetil-4-(4-fluorobencil)-2, 5-dimetilpiperazina (0,29 g, 1 mmol) en DMF anhidra (5 mL) se agregó 4- hidroxi-3-metoxifenilacetonitrilo (0,20 g, 1,2 mmol) y carbonato de potasio (0,28 g, 2 mmol, en polvo). La mezcla resultante se agitó a 50°C. Después de 15 horas el análisis por HPLC analítica (HPLC en una columna vydac de C18 con 20-70% acetonitrilo en gradiente de agua con 0,1% trifluoroacético acid) mostró que se había producido el consumo total de material de partida. La mezcla se virtió en agua y se extrajo con tres porciones de acetato de etilo. Los ex-

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tractos orgánicos combinados se lavaron en forma consecutiva con solución de KOH acuoso 0,5 N, agua, luego salmuera. Luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar un aceite amarillo. Éste se disolvió en acetato de etilo y se trató con una solución de HCl en éter anhidro La filtación del sólido resultante dio 0,38 g (85% de rendimiento) de (2*R*,5*S*)-1-((4-(ciano)metil-2-metoxifenoxi)metil)carbonil-4-(4-clorobencil)-2,5- dimetilpiperazina, sal de ácido clorhídrico como un sólido blanco RMN (DMSO- d_6) 11,5 (br s, 1), 7,6 (m, 4), 6,9 (m, 3), 4,8 (br s, 2), 4,4 (br s, 3), 4,0 (m, 1), 3,9 (s, 2), 3,8 (s, 3), 3,6 (m, 1), 3,3 (m, 2), 3. 2-2,9 (m, 3) ppm.

B. en forma similar, se prepararon otros compuestos de fórmula (Ia):

(*trans*)-1-((4-fluoro-3-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; RMN (DMSO-d_6) 10,4 (br d, 1), 7,7 (m, 2), 7,2 (m, 4), 6,9 (br s, 1), 5,0 (m, 1), 4,8 (m, 2), 4,3 (m, 3) , 3 7 (m, 2), 3,3 (m, 2), 2,9 (m, 1), 1,4-1,2 (m, 6) ppm;

1-((2-acetilaminofenoxi)metil)carbonil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,6 (br s, 1), 9,4 (s, 1), 8,0 (d, 1), 7,8 (br s, 2) , 7,2 (t, 2), 6,9 (m, 3), 5,0 (m, 3), 4,3 (m, 3), 3,8 (q, 1), 3. 6 (br s, 1), 3 4 (m, 1), 2,8 (m, 1), 2,1 (s, 3), 1,3 (dd,

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3), 1,2 (d, 3) ppm,

1-((3,4,5-trimetoxıfenoxı)metıl)carbonıl-2- (metoxıcarbonıl)metıl-4-(4-fluorobencıl)pıperazına,

1-((3,4,5-trımetoxıfenoxı)metıl)carbonıl-2-(etoxicarbonıl)-4-(4-fluorabencıl) pıperazına;

(*cis*)-1-((3,4,5-trimetoxıfenoxı)metıl) carbonıl-2,6-dımetıl-4-(4-fluorobencıl)pıperazına; RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (t, 2), 6,2 (s, 2), 4,7-4. 2 (m, 4), 3,8 (m, 9), 3,5 (s, 2), 2,6 (d, 2), 2,2 (dd, 2), 1,3 (m, 6) ppm;

1-((3,4,5-trımetoxıfenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencil)piperazına; RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (t, 2), 6,2 (s, 2), 4,6 (s, 3), 4,4 (m, 1), 4,1 (m, 1), 3,8 (s, 6), 3,85 (s, 3), 3,5 (m, 2), 2,8 (d, 1), 2,6 (d, 1), 2,1 (m, 2), 1,3 (m, 3) ppm;

1-((4-clorofenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl) pıperazına; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (s, 2), 4,4 (m, 1), 4,1 (m, 1), 3,7 (m, 1), 3,4 (m, 2), 2,8 (m, 1), 2. 6 (d, 1), 2,0 (m, 2), 1,3 (m, 3) ppm;

1-((4-clorofenoxı)metıl)carbonil-3-metıl-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (s, 2) , 4,0 (m, 2), 3,7 (m, 1), 3,4-2,9 (m, 3), 2,7 (m, 1), 2,5 (m, 1), 2,1 (m, 1) , 1,1 (m, 3) ppm;

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(2*S*)-1-((4-clorofenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina;

(2*R*)-1- ((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (s, 2), 4,4 (m, 1), 4,1 (m, 1), 3,7 (m, 1), 3,4 (m, 2), 2,8 (m, 1), 2,6 (d, 1), 2,0 (m, 2), 1,3 (m, 3) ppm,

4-((4-chiorofenoxi)metil)carbonil-3-(((4-clorofenil)amino)carbonil)metil-1-(bencil)piperazin-2-ona;

1-((fenoxi)metil)carbonil-2-etil-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-hidroximetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,7-4,5 (m, 3), 4,2-3,3 (m, 5), 3,2-2,7 (m, 2), 2. 3- 2,0 (m, 4) ppm;

1-(1-(4-clorofenoxi)-1-metiletil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(2*S*,5*R*)-1-((4-cloro-3,5-dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (t, 2), 6,2 (s, 2), 4,6 (m, 34), 4,2 (m, 1), 3,8 (m, 6), 3,5 (m, 3), 3,0 (m, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 4), 0,9 (m, 3) ppm;

(2*R*,5*S*)-1-((4-cloro-3,5-dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (t, 2), 6,2 (s, 2), 4,6 (m, 3), 4,2

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(m, 1), 3,8 (m, 6), 3. 5 (m, 3), 3,0 (m, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-3,5-dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (t, 2), 6,3 (s, 2), 4,7 (m, 2), 4,2 (m, 1), 3,8 (s, 6), 3,5 (m, 4), 3,0 (m, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(2*S*,5*R*)-1-((4-bromo-3,5-dimetoxifenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal clorhidrato; RMN (DMSO-d_6) 10,7 (d, 1), 7,8 (m, 2), 7,3 (m, 2), 6,3 (s, 2), 4,9 (m, 2), 4,3 (m, 2), 4,0-2,8 (m, 12), 1,4-1,2 (m, 6) ppm,

(2*S*,5*R*)-1-((4-nitro-3-formilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10,4 (s, 1), 8,2 (d, 1), 7,3 (m, 4), 7,0 (t, 2), 4,8 (m, 3), 4,2-2,3 (m, 7), 1,3 (m 3), 1,0 (m, 3) ppm,

(*trans*) -1-((4-cloro-2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; RMN ($CDCl_3$) 9,2 (br s, 1), 8. 2 (s, 1), 7,4 (m, 3), 7,0 (t, 2), 6,8 (d, 1), 5,9 (s, 1), 5,0-4,0 (m, 3), 3. 8-3,0 (m, 5), 2,8 (d, 1), 2,3 (d, 1), 1,3 (m, 3), 1,0 (br s, 3) ppm,

(2*R*,5*S*)-1-((4-cloro-2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,2 (br s, 1), 8,2 (s, 1), 7,4 (m, 4), 7,0

(t, 2), 6,8 (d, 1), 5,8 (s, 1), 4,7 (m, 2), 3,7-3,1 (m, 5), 2,8 (d, 1), 2,3 (d, 1), 1. 3 (d, 3), 1,0 (br s, 3) ppm;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((amino)carboniloxi)metil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-3- nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal clorhidrato; RMN (DMSO-d_6) 11 (br d, 1), 7,9 (br s, 1), 7,6 (m, 2), 7,3 (m, 4), 5,2 (d, 1), 5,0 (m, 2), 4,3 (m, 4), 4. 0 (m, 1), 3,6 (m, 2), 1,3 (m, 6) ppm;

(*trans*)-1-((4- cloro-2-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina, sal clorhidrato; RMN (DMSO-d_6) 10,9 (br d, 1), 7,9 (br s, 2), 7,6 (m, 1), 7,3 (m, 4), 5,0 (m, 2), 4,5 (s, 2), 4,3 (m, 2), 3,7-3,3 (m, 6), 1,3 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina, sal diclorhidrato; RMN (DMSO-d_6) 7,7 (br s, 3), 7,3 (m, 5), 5,2 (d, 1), 5,0 (m, 2), 47-4,2 (m, 4), 3,9-3,4 (m, 3), 1,3 (m, 6) ppm,

(*trans*)-1-((2- (aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 9,1 (br s, 1), 8,2 (d, 1), 7,4 (dd, 1), 7. 3 (br s, 2), 7,1 (t, 1), 7,0 (m, 2), 6,9 (d, 1), 5,8 (br s,

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1), 4,7 (m, 2) , 4,2 (m, 1), 3,7-3,4 (m, 3), 3,0 (br s, 1), 2,7 (br s, 1), 2,3 (d, 1), 1. 3 (m, 3), 1,0 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-amino-5- nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal diclorhidrato, RMN ($CDCl_3$) 10,9 (br d, 1), 7,8 (m, 2), 7,5 (dd, 1), 7,3 (m, 2), 6,8 (s, 1), 5,0 (m, 3), 4,3-3,2 (m, 7), 1,4- 1,2 (m, 6) ppm;

(*trans*)-1-((4-metil-2-formilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal clorhidrato, RMN (DMSO-d_6) 10,9 (br d, 1), 10,4 (s, 1), 7,9 (s, 2), 7,5 (m, 2), 7,3 (m, 2), 7,0 (d, 1), 5,2 (m, 1), 5,0 (m, 2), 4,6 (m, 1), 4,3 (m, 3), 3,6 (m, 2), 2,8 (m, 1), 2,5 (s, 3), 1,4-1,1 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-formilfenoxi)metil)carbonil- 2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10,9 (br d, 1), 10,4 (s, 1), 7,8 (s, 1), 7,5 (dd, 1), 7,3 (dd, 2), 7,0 (m, 3), 4,8 (m, 3), 4,1 (m, 1), 3,5 (m, 3), 3,0 (br s, 1), 2,7 (dd, 1), 2. 5 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

(*trans*)-1-((2- metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina sal clorhidrato; RMN (DMSO-d_6) 11,0 (d, 1), 7,8 (t, 2), 7,3 (t, 2), 7,1 (m, 2), 6,8 (m, 2), 4,9-3,3 (m, 9), 2,8 (t, 1), 2,2 (s, 3) , 1,4-1,1 (m, 6) ppm;

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(*trans*)-1-((2-(hidroximetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal clorhidrato, RMN (DMSO-d_6) 11,0 (d, 1), 7,8 (t, 2), 7,3 (m, 3), 7,1 (t, 1), 6,9 (m, 2), 5,0-3,2 (m, 11), 2,8 (t, 1), 1,4- 1,1 (m, 6) ppm,

(*trans*)-1-((3-cloro-5-metoxifenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal clorhidrato; RMN (DMSO-d_6) 10,8 (d, 1), 7,8 (m, 2), 7,3 (t, 2), 6,6 (s, 2), 6,5 (br s, 1), 5,0-3,2 (m, 12), 2,8 (m, 1), 1,4-1,2 (m, 6) ppm,

(*trans*)-1-((2-metoxi-5-nitrofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal clorhidrato, RMN (DMSO-d_6) 11,1 (d, 1), 7,9 (m, 2), 7,7 (br s, 1), 7,2 (m, 4), 5,2-3,3 (m, 12), 2,8 (t, 1), 1,4-1,2 (m, 6) ppm;

1-((fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina, RMN (DMSO-d_6) 11 (br d, 1), 7,7 (m, 2), 7,3 (m, 4), 6,9 (m, 3), 4. 9 (m, 3), 4,3 (m, 3), 4,0-2,8 (m, 5), 1,4 (d, 1,5), 1,2 (d, 1,5) ppm;

(*trans*)-1-((4-clorofenilamino)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina, RMN (DMSO-d_6). 7,4 (dd, 2), 7,1 (m, 4), 6,6 (d, 2), 5,8 (t, 1), 4,5 (br s, 0,5), 4,0 (br m, 1,5), 3,8 (br m, 1), 3,8-3,3 (m, 3), 3,0 (m, 2), 2,6 (m, 1), 2,2 (d, 1), 1,1 (br d, 3), 0,9 (br d, 3) ppm;

(*trans*)-1-((4-cloro-3-nitrofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11 (br d, 1), 7,7 (m, 4), 7,3 (m, 3), 5,0 (q, 2), 4,7 (m, 0,5), 4,4 (m 2,5), 3,8 (m, 0,5), 3,6-2,9 (m, 6), 1,4 (d, 1,5), 1. 3 (d, 1,5) ppm;

(*trans*)-1-((4-cloro-2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,8 (br d, 1), 7,9-6,8 (m, 7), 5,1-2,8 (m, 10), 2,2 (s, 3), 1,3 (m, 6) ppm,

(*trans*)-1-((4-cloro-2-(dietilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina, RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (t, 2), 6,8 (m, 3), 4,8 (br s, 3) 4,1 (br s, 1), 3,5 (q, 3), 3,2 (q, 4), 3,0 (br s, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (br s, 3), 1 (m 9) ppm;

(*trans*)-1-((4-cloro-2-hidroxifenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 2), 7. 0-6,7 (m, 5), 4,9 (m, 0,5), 4,6 (br s, 2), 4,2 (m, 0,5), 3,6-3,2 (m, 3), 3,0 (br d, 1), 2,7 (br d, 1), 2,2 (d, 2), 1,3 (m, 3), 0,9 (m, 3) ppm;

1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2-metil-4- (4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,8 (d, 1), 7,7 (m, 2), 7,3 (m, 4), 6,9 (d, 1), 5,0-4,3 (m, 6), 3,9-2,9 (m, 7), 1,4 (d, 1. 5), 1,2

(d, 1,5) ppm;

(2*R*,5*S*)-1-((4-cloro-3-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0-6,7 (m, 3), 4. 7 (m, 4), 4,1 (m, 1), 3,5 (m, 2,5), 3,2 (m, 0,5), 3,0 (s, 1), 2,7 (dd, 1), 2,2 (d, 1), 2,1 (m, 1), 1,2 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(ureidometil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 7,4 (m, 2), 7,1 (m, 4), 6,9 (d, 1), 6,4 (t, 1), 5,6 (s, 2), 5,0-4,0 (m, 4) , 3,5 (m, 2), 3,3 (d, 2), 3,0 (m, 2), 2,2 (m, 2), 1,2 (br d , 3), 0,9 (br d, 3) ppm;

1-((4-cloro-2-aminofenoxi)metil)carbonil-2-metil- 4-(4-fluorobencil)piperazina, RMN (DMSO-d_6) 11,2 (br d, 1), 7,7 (m, 2), 7,3 (t, 2), 6,9 (m, 3), 5,0-4,2 (m, 5), 3,9 (m, 1), 3. 6 (m, 1), 3,4 (m, 1), 3,0 (m, 3), 1,4 (d, 1,5), 1,3 (d, 1,5) ppm;

1-((4-cloro-3-aminofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,2 (br d, 1), 7,8 (br s, 2), 7,3 (t, 2), 7,0 (d, 1), 6,4 (s, 1), 6,2 (d, 1), 4,8-4,2 (m, 5), 4,0 (m, 1), 3,6 (m, 1), 3,4 (d, 1), 3,2-2,9 (m, 4), 1,3 (m, 3) ppm;

(2*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9. 0

(s, 1), 8,2 (s, 1), 7,3 (t, 1), 7,0 (t, 3), 6,8 (q, 3), 5,0 (s, 2), 4,6 (dt, 2), 4,4 (d, 0,5), 3,7 (br s, 0,5), 3,4 (m, 2,5), 3,0 (t, 0,5), 2,8 (m, 1), 2,6 (d, 1), 2,1 (m, 3), 1,4 (d, 1,5), 1,3 (d, 1,5) ppm;

(2*R*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4- fluorobencil)piperazina; RMN ($CDCl_3$) 9,0 (s, 1), 8,2 (s, 1), 7,3 (t, 1), 7,0 (t, 3), 6,8 (q, 3), 5,0 (s, 2), 4,6 (dt, 2), 4,4 (d, 0,5), 3,7 (br s, 0,5), 3,4 (m, 2,5), 3,0 (t, 0,5), 2,8 (m, 1), 2,6 (d, 1), 2,1 (m, 3), 1,4 (d, 1,5), 1,3 (d, 1,5) ppm;

(*trans*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; RMN (DMSO-d_6) 10,8 (br s, 1), 8,2 (br s, 2), 7,8 (br s, 2), 7,7 (br s, 1), 7,3 (m, 2), 6,8 (br s , 2), 5,2- 4,3 (m, 5), 3,9-3,1 (m, 5), 2,8 (t, 1), 1,5-1,1 (m, 6) ppm;

(2*R*,5*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9. 0 (s, 1), 8,3 (s, 1), 7,3 (t, 1), 7,0 (t, 3), 6,8 (m, 3), 5,0 (s, 2), 4,6 (m, 2), 4,2 (d, 0,5), 3,7-3,4 (m, 2,5), 3,2 (m, 2), 2,7 (d, 1), 2,5(m, 1), 2,2 (d, 1), 1,3 (br d, 3), 1,0 (br d, 3) ppm,

(*trans*)-1-((4-bromo-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 10,4 (s, 1), 8,0 (s, 1), 7,6 (dd, 1), 7,3 (m, 2), 7,0 (m, 3), 4,8 (m, 3), 4,1 (br d, 1), 3,5 (m, 3),

3. 0 (m, 1), 2,7 (dd, 1), 2,3 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

1-((4-cloro-2-metoxicarbonilfenoxı)metıl)carbonil-2-metıl-4-(4- fluorobencıl)pıperazına, RMN (DMSO-d_6) 11,0 (br d, 1), 7,7 (m, 3), 7,6 (dd, 1), 7,3 (t, 2), 7,0 (d, 1), 5,0 (do, 2), 4,7 (m, 1), 4,4 (m, 3), 3,8 (m, 4), 3,4 (m, 2), 3,0 (m, 2), 1,4 (d, 1,5), 1,2 (d, 1. 5) ppm,

(*trans*)-1-((4-cloro-2-metoxıcarbonılfenoxi) metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)piperazına; RMN ($CDCl_3$) 7,9 (br s, 2), 7,8 (s, 1), 7,4 (m, 1), 7,1 (t, 2), 7,0 (d, 1), 4,8 (m, 3), 4,4 (m, 2), 3,9 (m, 4), 3,5 (m, 2), 2,8 (m, 2), 1,6 (m, 3) , 1,3 (m, 3) ppm;

1-((4-cloro-2-amınocarbonılfenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)pıperazına; RMN ($CDCl_3$) 9,6 (br s, 1), 8,0 (s, 1), 7,6 (dd, 1), 7,4 (dd, 2), 7. 2 (t, 2), 6,9 (d, 1), 5,0 (m, 3), 4,4 (m, 2), 4,0 (m, 1), 3,8 (m, 2), 3,6 (m, 1), 3,1 (m, 1), 2. 9 (m, 1) , 1,6 (d, 1,5), 1,4 (d, 1,5) ppm,

1-((4-cloro-2-(amınocarbonıl) fenılamıno)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)piperazına; RMN (DMSO-d_6) 11,2 (br s, 1), 7,9 (br s, 1), 7,7 (m, 3), 7,2 (m, 2), 6,6 (d, 1), 4,8 (br s, 1), 4,4-3,9 (m, 6), 3,4 (d, 1), 3,0 (m, 3), 1,4 (m, 3) ppm;

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(2*R*)-1-((4-cloro-2-aminocarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 9,1 (s, 1), 8,2 (s, 1), 7,4 (dd, 1), 7,3 (m, 3), 7,0 (t, 2), 6,8 (d, 1), 5,8 (br s, 1), 4,8 (m, 3), 3. 5 (m, 3), 2,9 (d, 1), 2,7 (d, 1), 2,2 (m, 2), 1,4 (d, 1,5), 1,3 (d, 1,5) ppm,

1-((4-cloro-2-formilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,0 (br d, 1), 10,4 (s, 1), 7,6 (m, 4), 7,3 (t, 2), 7,2 (d, 1), 5,2 (m, 2), 4,7 (m, 1), 4,3 (m, 3), 3,9 (m, 1), 3,6 (m, 1), 3,1 (m, 3), 1,5 (d, 1,5), 1,3 (d, 1,5) ppm;

(2*R*,5*S*)-1-((4-cloro-2-formilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10,5 (s, 1), 7,8 (s, 1), 7,5 (d, 1), 7,3 (m, 2), 7,0 (t, 3), 4,8 (m, 3), 41 (m, 1), 3,5 (m, 3), 3,1 (br s, 1), 2,7 (dd, 1), 2 3 (dd, 1), 1,3 (m, 3), 0,9 (m, 3) ppm,

(2*R*)-1-((4-cloro- 2-formilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 10,4 (s, 1), 7,8 (s, 1), 7,5 (d, 1), 7,3 (m, 2), 7,0 (t, 3), 4,8 (br s, 2), 4,7 (m, 1), 4,2 (m, 1), 3,4 (m, 3), 3. 1 (m, 1) , 2,8 (br d, 1), 2,6 (br d, 1), 2,1 (m, 1), 2,0 (dd, 1), 1,3 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-cianofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$)

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7,5 (dd, 1), 7,3 (m, 2), 7,0 (m, 4), 4,8 (m, 3), 4,1 (m, 1), 3,5 (m, 3), 3,0 (m, 1), 2,7 (m, 1), 2,2 (m, 1), 1,3 (m, 3), 0,8 (m, 3) ppm,

(*trans*)-1-((4-cloro-2-acetilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,8 (br d, 1), 7,8 (s, 2), 7,5 (m, 2), 7,3 (m, 3), 7. 2 (m, 1), 5,3 (m, 1), 5,0 (s, 2), 4,3 (m, 3), 4,0 (m, 1), 3,8-3,3 (m, 2), 2. 8 (m, 1), 2,6 (s, 3), 1,4 (dd, 3), 1,3 (m, 3) ppm;

1-((2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6) 11,0 (br s, 1), 9,4 (s, 1), 8,0 (d, 1), 7,6 (d, 2), 7,3 (t, 2), 7,0 (m, 3), 4,9 (q, 2), 4,7 (m, 1), 4. 3 (m, 3), 3,9 (m, 1), 3,6-2,8 (m, 4), 2,1 (s, 3), 1,4 (d, 1,5), 1,3 (d, 1. 5) ppm,

(*trans*)-1-((3-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,0 (br d, 1), 7,9 (s, 2), 7,5-7,3 (m, 6), 5,2 (d, 1), 4,9 (m, 2), 4,3 (m, 3), 3,6 (m, 2) , 3,2 (m, 1), 2,8 (m, 1), 1,5-1,2 (m, 6) ppm;

(2*R*, 5*S*)-1-((3-hidroxi-5-metilfenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina; RMN (DMSO-d_6)10,5 (br d, 1), 9,3 (s, 1), 7,8 (s, 2), 7,2 (m, 2), 6,2 (s, 2), 6,1 (s, 1), 4,7 (m, 4) , 4,3 (m, 3), 3,8 (m, 1), 3,6 (m, 1), 2,8 (m, 1), 2,2 (s, 3), 1,4

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(m, 3), 1,2 (m, 3) ppm,

(*trans*)-1-((4-metil-2-aminofenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO- d_6) 11,0 (br m, 1), 7,8 (s, 2), 7,2 (m, 5), 5,3 (m, 1), 5. 0 (m, 2), 4,3 (m, 3), 4,0 (m, 1), 3,5 (m, 2), 2,8 (m, 1), 2,2 (s, 3), 1,3 (m, 6) ppm,

(*trans*)-1-((3-formilfenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina, RMN (DMSO-d_6) 11,0 (br d, 1), 10,0 (s, 1), 7,9 (s, 2), 7,5 (m, 2), 7,3 (m, 3), 6,9 (m, 1), 5. 2 (m, 1), 4,9 (m, 2), 4,3 (m, 3), 4,0 (m, 1), 3,6 (m, 2), 2,8 (m, 1) , 1,3 (m, 6) ppm;

(*trans*)-1-((4-metil-2-acetilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,5 (s, 1), 7,3(m, 3), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 3), 4,2 (br d, 1), 3,6 (m, 1), 3,5 (q, 2), 3,0 (br s, 1), 2,7 (m, 4), 2. 2 (m, 4), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((2- metoxicarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 12,1 (s, 1), 7,8 (m, 3), 7,3 (br s, 1), 7,0 (br s, 4), 4,8 (m, 2), 4,3 (m, 3), 3,9 (m, 5), 3,6 (m, 1), 2,8 (m, 1), 2,4 (m, 1), 1,6 (m, 3), 1,3 (m, 3) ppm;

(*trans*)-1-((3-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina, RMN (DMSO-d_6) 10,8 (br d, 1), 7,8 (m, 3), 7,7 (m, 1), 7,6 (t, 1), 7,4 (d,

1), 7,3 (t, 2), 5,2 (m, 1), 5,0 (m, 2), 4. 7 (m, 1), 4,3 (m, 3), 4,0 (m, 1), 3,6 (m, 1), 2,8 (m, 1), 1,4 (m, 3), 1,3 (m, 3) ppm,

(*trans*)-1-((4-acetil-2-(aminocarbonil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN (DMSO- d_6) 9,7 (br d, 1), 8,6 (s, 1), 8,5 (s, 1), 8,1 (d, 1), 7,8 (s, 1), 7,6 (br s, 3), 7,3 (t, 3), 5,4 (d, 1), 5,1 (m, 2), 4,6 (m, 1), 4. 3 (s, 2),4,2 (m, 1), 3,7 (m, 1), 3,4 (m, 1), 3,0 (m, 1), 2,6 (s, 3), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((4-nitro-3-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN (DMSO-d_6) 11,2 (br d, 1), 8,0 (m, 3), 7,3 (m, 2), 7,0 (m, 2), 5,3 (d, 1), 5,0 (m, 2) , 4. 3 (m, 3), 3,7-3,3 (m, 2), 3,0 (m, 1), 2,8 (m, 1), 2,6 (s, 3), 1,4 (m, 3), 1,3 (m, 3) ppm;

(*trans*)-1-((5-nitro-2-metilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO- d_6) 10,5 (br d, 1), 7,7 (m, 4), 7,4 (d, 1), 7,3 (t, 2), 5. 3 (d, 1), 5,1 (m, 2), 4,7 (m, 1), 4,3 (m, 2), 3,9 (q, 1), 3,6 (br d, 1), 3. 4 (m, 1), 2,9 (dd, 1), 2,3 (s, 3), 1,4 (m, 3), 1,3 (m, 3) ppm;

(*trans*)-1-((4-amino-3-nitrofenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina, RMN (DMSO-d_6) 11,2 (br d, 1), 7,9 (t, 2), 7,3 (m, 4), 7,0 (d, 1),

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4,8 (m, 3), 4,3 (m, 3), 3,9 (m, 1) , 3,6 (m, 1), 3,2 (m, 1), 2,8 (t, 1), 1,4 (dd, 3), 1,3 (dd, 3) ppm;

(*trans*)-1-((5-nitro-2-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,2 (br d, 1), 7,9 (t, 2), 7,7 (d, 1), 7,6 (s, 1), 7,3 (t, 2), 6,7 (d, 1) , 5. 0 (m, 3), 4,7 (m, 1), 4,3 (m, 2), 4,0 (q, 1), 3,6 (m, 1), 3,3 (m, 1), 2,8 (t, 1) , 1,4 (dd, 3), 1,3 (dd, 3) ppm;

(*trans*)-1-((2- aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,3 (m, 1), 7,9 (br s, 2), 7,8 (br m, 1), 7,3 (m, 4), 7,0 (t, 1), 5,3 (m, 1), 5,0 (m, 2), 4,6 (m, 1), 4,3 (m, 2) , 3,6 (m, 3), 2,8 (m, 1), 1,3 (m, 6) ppm;

(*trans*)-1-((3- metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,5 (br d, 1), 7,8 (s, 2), 7,3 (m, 2), 7,1 (t, 1), 6,5 (m, 3), 4,8 (m, 2), 4,3 (m, 3), 3,8 (m, 1), 3,6 (m, 1), 3. 4 (m, 2), 2,8 (t, 1), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)- 1-((4-metoxi-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,; RMN (DMSO-d_6) 11,2 (br s, 1) , 7,9 (br s, 2), 7,3 (m, 3), 7,1 (s, 2), 5,2 (d, 1), 4,9 (s, 2), 4,3 (m, 3), 3,9-3,4 (m, 9), 2,8 (m, 1), 1,4-1,2 (m, 6) ppm;

(*trans*)-1-((5-metoxi-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; RMN (DMSO-d_6)

11,2 (br d, 1), 7,9 (dd, 2), 7,6 (m, 1), 7,3 (t, 2), 6,6 (q, 2), 5,3 (d, 1), 5,0 (s, 2), 4,3 (m, 3), 3,8 (s, 3), 3,4 (m, 3), 2,8 (m, 1), 2,6 (s, 3), 1,5-1,2 (m, 6) ppm;

(*trans*)-1-((2-((2-hidroxietil)aminocarbonil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,8 (br d, 1), 9,1 (br s, 1), 7,9 (d, 1), 7,8 (br s, 2), 7,4 (t, 1), 7,2 (m, 3), 7,0 (t, 1), 5,2 (d, 1), 5,0 (m, 2), 4. 3 (m, 3), 3,9-3,4 (m, 7), 2,8 (dd, 1), 14-1,2 (m, 6) ppm,

(*trans*)-1-((2-((2-hidroxietoxi)carbonil)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,0 (br s), 7,7 (m, 3), 7,4 (t, 1), 7,3 (t, 2), 7,0 (dd, 2), 5,0 (m, 2), 4,5 (m, 1), 4,2 (m, 5), 3,8 (q, 1), 3,6 (t, 2), 3,4 (m, 2) , 2,9 (m, 1), 1,3 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((2-(2-hidroxietoxi)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; RMN (DMSO-d_6) 10,5 (br d, 1), 7,8 (t, 2), 7,3 (t, 2), 6,9 (m, 4), 4,8 (m, 3), 4,4 (m, 1), 4,3 (m, 2), 3,9 (m, 3), 3,6 (m, 3), 3,4 (m, 1), 2,8 (m, 1), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((2-acetil-4,5-dimetilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,4 (br s, 1), 7,8 (m, 2), 7,4 (s, 1), 7,2 (t,

2), 6 8 (m, 1), 5,2 (d, 1), 4,9 (s, 2), 4,3 (m, 3), 3,8 (m, 1), 3,6 (m, 1), 3,4 (m, 1), 2,8 (m, 1), 2,6 (s, 3), 2,2 (s, 3), 2,1 (s, 3), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((5-metoxi-2-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11,0 (br d, 1), 7,9 (br s, 2), 7,7 (d, 1), 7,3 (m, 2), 6,6 (m, 2), 5,0 (m, 3), 4,3 (m, 3), 3,8 (s, 3), 3,7 (s, 3), 3. 6 (m, 1), 3,4 (m, 2), 2,8 (dd, 1), 1,4 (dd, 3), 1,2 (dd, 3) ppm;

1-((4-clorofenilamino)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6) 7,4 (t, 2), 7,15 (t, 2), 7 1 (d, 2), 6,6 (d, 2), 5,8 (t, 1), 4,5 (m, 1), 4,2 (m, 1), 3,9 (m, 1), 3,7 (m, 1), 3,4 (m, 1), 3,3 (m, 1), 2,9 (m, 1), 2,8 (d, 1), 2,6 (d, 1), 2,0 (m, 2), 1,3 (d, 1,5), 1,1 (d, 1,5) ppm;

(*trans*)-1-((benzo[b]piran-2-on-7-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,6 (d, 1), 7,4 (d, 1), 7,3 (m, 2), 7,0 (m, 3), 6,8 (s, 1), 6,3 (d, 1), 4,7 (m, 3), 4,1 (m, 1) , 3,6 (m, 3), 3,0 (br s, 1), 2,7 (br d, 1), 2,2 (d, 1), 1,3 (m, 3), 1,0 (m, 3) ppm;

(*trans*)-1-((2-cloro-4-carboxifenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((1-nitroso-3,6-di(hidroxisulfonil)naftalen-2-

iloxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((2-nitroso-4-hidroxisulfonilnaftalen-1-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3,6-di(hidroxisulfonil)naftalen-1-iloxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-hidroxisulfonil-6-aminonaftalen-1-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-hidroxisulfonil-7-aminonaftalen-1-iloxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((5-hidroxisulfonilquinolin-8-iloxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,3-dinitro-7-hidroxisulfonilnaftalen-1-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-carboxi-4-hidroxisulfonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-amino-4-hidroxisulfonilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-formil-2,6-di-*t*-butilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

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(trans)-1-((4-(morfolin-4-il)metil-2,5-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(metoxicarbonil)-2,6-diclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(hidroxisulfonil)naftalen-1-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,6-di(hidoxisulfonil)-8- aminonaftalen-1-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-carboxi-5-aminofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((4-trifluro metil-2,3,5,6,-tetrafluorofenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2- metoxi-4-formil-5-(2-hidroxi-3-metoxi-5-formilfenil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-carboxi-2,3,5,6-tetrafluorofenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-(adamant-1-il)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-(adamant-1-il)-4- metilfenoxi)metil)carbo-

nil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,4-di((1-metil-1-fenil)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-acetil-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-nitro-4-t- butilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-acetil-4-cloro-5-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-acetil-4-cloro-6-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-acetil-4,6- dibromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-formil-4,6-di(*t*-butil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((3,5-dinitrofenoxi)metil)carbonil-2,5-dimethyt-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2,6-dicloro-4-etoxicarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-etoxicarbonil-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-6-(prop-3-enil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-fluoro-4-cianofenoxi)metil)carbonil-2,5-

dımetıl-4-(4-fluorobencıl) pıperazina,

(trans)-1-((2-acetıl-4-metıl-6-nıtrofenoxi) metıl)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazina;

(trans)-1-((2-metılbenzotıazol-5-ıloxı)metıl)carbonıl-2,5-dımetıl- 4-(4-fluorobencıl)pıperazina;

(trans)-1-((2-carboxı-4-(hıdroxısulfonıl)fenoxı)metil) carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıpe-razına;

(trans)-1-((4-(4-(trifluorometıl)fenoxı)fenoxı)metıl) carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((2-(1*H*-pirazol-3-il)-4-cloro-5-metılfenoxı) metil)carbonil-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((2-(1*H*-pırazol-3-ıl)-4-clorofenoxi)metil)carbonıl-2,5-dimetil-4- (4-fluorobencıl)pıperazına;

(*trans*)-1-(((2-fenıl-4-oxo-7- hıdroxı-4*H*-1-benzopiran-3-ıl)oxı)metıl)carbonıl-2,5-dimetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-cloro-3- trifluorometilfenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl) pıperazına;

(*trans*)-1-((2-metoxı-4-(butoxımetıl)fenoxı) metil)carbonıl-2,5-dımetıl-4-(4-fluorobencil)piperazına;

(*trans*)-1-((6-hidroxiquınolın-2-ıloxı)metıl)carbonıl-2,5-dımetıl-4- (4-fluorobencıl)pıperazına,

(*trans*)-1-((2-metoxıcarbonıl-6-metoxıfenoxı)metıl)carbonil-2,5-dimetıl-4-(4-fluorobencıl) pıperazına;

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(*trans*)-1-((2,5-di(*t*-butil)-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-formil-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(2*H*-benzotriazol-2-il)-4-(2-hidroxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((2-(metiltio)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3,5-di(*t*-butil)-4-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((3,5-dibromo-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2,6-diiodo-4-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-nitro-4-metoxicarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((2-(etoxicarbonil)indol-5-iloxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*) -1-((3-(2-carboxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2,6-dinitro-4-(carboximetil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

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(trans)-1-((2-nitro-3-carboxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((6-carboxinaftalen-2-iloxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,6-difluoro-4-etilcarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-(2-(metoxicarbonil)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(prop-3-enil)-4-acetilfenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((3-oxo-2*H*-benzofuran-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,4,6-tribromo-3,5-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(heptilcarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((2-nitro-4-fenilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-(eth-2-enil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-cloro-4-metoxicarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((2,6-diiodo-4-cianofenoxi)metil)carbonil-2,5-

dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-diiodo-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-fenil-4-oxo-4*H*-1-benzopiran-5-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-fenil-4-oxo-7-metoxi-4*H*-1-benzopiran-5-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-fenil-4-oxo-7-metoxi-2,3-dihidro-4*H*-1-benzopiran-5-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-octilcarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((4-ftalimid-1-ilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((3-(morfolin-4-il)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3-cloro-4- bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-oxo-7-metoxi-2*H*-1-benzopiran-8-il) oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((2-acetil-5-fluorofenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

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(*trans*)-1-((2-(1-metilciclohex-1-il)-4-metil-6-(2-hidroxi-3-(1-metilciclohex-1-il)-5-metilbencil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-formil-3-metoxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((2-amino-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-cloro-4-carboxi-6-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2,6-dimetil-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-(2-(carboxi)etil)fenoxi)metil) carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,6-dimetoxi-4-hidroximetil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dibromo-4-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-nitro-4-(etoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-amino-4-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(2-(4-nitrofenil)eth-2-enil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((2-acetil-3,5-dimetoxifenoxi)metil)carbonil-

2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,6-di(*t*-butil)-4-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4- (etoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-ciclohexil-4- clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dimetil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-etilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-*n*-butilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((3-carboxi-1-bromonaftalen-2-il)oxi)metil) carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-bromo-4-nitro-6-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-formil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dicloro-4-(etoxicarbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((4-metil-2-oxo-2*H*-1-benzopiran-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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(trans)-1-((2,3-dıbromo-4-formıl-6-metoxıfenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)piperazına;

(trans)-1-((4-(2-(4-nitrofenıl)eth-2-ıl)fenoxı)metil) carbonıl-2,5-dimetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2,4,6-trıbromo-3- formılfenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((2-bencıl-4-clorofenoxi)metil)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((2- (bezotıazol-2-ıl)fenoxı)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2-nıtro-6-fluorofenoxı)metil) carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(trans) -1-((2-etoxı-4-metılfenoxı)metil)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-bromo-4,6-dı(*t*-butıl)fenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2-(pırrolıdin-1-ıl)fenoxı)metıl) carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(trans) -1-((2-(morfolın-4-ıl)fenoxi)metıl)carbonıl-2,5-dımetil-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-(pıperıdın-1-ıl) fenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-formil-4-cloro-6-bromofenoxı)metıl)carbonıl-2, 5-dimetıl-4-(4-fluorobencıl)pıperazına;

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(trans)-1-(((4,7-dimetoxi-5-formilbenzofuran-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-oxo-4-metil-8-nitro-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-cloro-4-bromo-6-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,4-dimetil-6-t-butilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-nitro-4-(hidroxisulfonil)naftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((3-(hidroxisulfonil)-6-aminonaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((3-(hidroxisulfonil)-7-aminonaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((3-(metoxicarbonil)naftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4-(hidroxisulfonil)fenoxi)metil)

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carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-*n*-butilcarbonilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-etoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-(((2-etil)hexoxi)carbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-((*n*-pentoxi)carbonil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-nitro-5-(metoxicarbonil)fenoxi)metil)carbonil- 2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2, 4,6-tribromo-3-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-metoxi-5- metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-metoxi-4-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(2- (fenil)eth-2-enil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-(1,2,4-triazol-1-il)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-nitro-4-cloro-5-metilfenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(*n*-hexoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina,

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(trans)-1-((2-cloro-4-formil-6-metoxifenoxi)metil)car--bonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-metoxi-4-(2-(etoxicarbonil) etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3,4,6-tetraclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-((2-metilpropoxi)carbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-(*n*-butoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-(fenilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-hidroximetil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2-mercaptofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina:

(trans)-1-((2-nitro-6-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,4-di(1-metilbutil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-trifluorometil-4-nitrofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dibromo-4-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)pipe-

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razina;

(trans)-1-((2,4-dicloro-6-acetil)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxicarbonil-4-metilfenoxi)metil)carbonil- 2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-formil-4-bromo-6-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,6-diformil-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dinitro-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-nitro-4-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-formil-4-nitro-6-metoxifenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((4-(aminocarbonil)metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxicarbonil-4-metoxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-fenil-4-oxo-4*H*-1-benzopiran-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-cloro-4-trifluorometilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-carboxi-3-metil-6-isopropilfenoxi)metil)

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carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((5,7-dibromo-2-metilquinolin-8- il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((5,7-dicloro-2-metilquinolin-8-il)oxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dinitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-nitro-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-amino-4-(1,1-dimetilpropil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-difenil-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,4-dicloro-3-metil-6-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((2-oxo-4-(carboxi)metil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((2-oxo-4-trifluorometil-2*H*-1-benzopiran-7-ilo)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-*t*-butil-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-formil-6-metilfenoxi)metil)carbonil-2,5-

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dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2-metoxicarbonil-4-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-bromo-5-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,4-di(1,1-dimetilpropil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-metil-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3,4-trifluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2,5-difluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metil-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-metil-3-(etoxicarbonil)indol-5-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-aminocarbonil-4-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dinitro-3-*t*-butilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-fluoro-4-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-carboxi-3-fluorofenoxi)metil)carbonil-2,5-

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dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(2-etilhexoxi)carbonilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,4,6-tribromo-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((4-(4-bromofenil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(4-carboxifeny)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,3,6-trifluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,4,5-trifluorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,4,6-trifluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-fluoro-5-trifluorometilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2,4-dinitronaftalen-1-il)oxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((3,6-di(hidroxisulfonil)-8-aminonaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-acetil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,6-dimetil-4-(1-(3,5-dimetil-4-hidoxi-

fenil)-1-metiletil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-(3-(4-hidroxifenil)hex-2-il)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((6-(hidroxisulfonil)naftalen-2-il)oxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-cloro-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-bromo-4,5-difluorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-cloro-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-metoxi-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(2-(metoxicarbonil)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,6-difenil-4-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-amino-3-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-metil-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metil-4-iodofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-fluoro-6-metoxifenoxi)metil)carbonil-2,5-

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dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-3-isopropil-6-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-3,4,6-triclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-6-isopropilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-(piperidin-1-il)-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2,3-dihidro-2,2-dimetilbenzofuran-7-il)oxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-di(*t*-butil)-4-(1-metilpropil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-metil-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-(((fenanthren-9-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-nitro-4-bromofenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2-fluoro-3-trifluorometilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-nitro-5-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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(trans)-1-((2-cloro-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-formil-4-bromo-6-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-(acetil)metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(5-mercaptotetrazol-1-il)fenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(trans)-1-((2,4,6-triiodo-3-(2-carboxi)butilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-hidroximetil-4-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3,5,6-tetrafluoro-4-(2,3,4,5,6-pentafluorofenil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(benzotriazol-2-il)-4,6-di(1,1-dimetilpropil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-fenil-3-hidroxi-4-oxo-4*H*-1-benzopiran-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((indanonil)oxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-nitro-4-(hidroxisulfonil)fenoxi)metil)car-

bonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2-nıtro-3-metılfenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(trans) -1-((4-(2,4-dınıtrofenıl)amınofenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazina;

(trans)-1-((3-metıl-4-nitrofenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazina,

(trans)-1-((2,6-dıbromo-4-nitrofenoxi)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazina,

(trans)-1-((2,6-dıiodo-4-nıtrofenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencil) pıperazına:

(trans)-1-((2-formıl-4-nıtrofenoxi)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-amınofenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2-amıno-5-nıtrofenoxı)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazina;

(trans)-1-((2-amıno-5-metılfenoxı)metıl)carbonil-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-amino-4-clorofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)piperazina;

(trans)-1-((2-amino-4-carboxıfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-amıno-4-t-butilfenoxı)metıl)carbonıl-2,5-dimetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-amino-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metil-3-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-5-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3-metil-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,5-dimetil-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dibromo-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-aminocarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-aminocarbonil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(2-aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,4,6-tri(dimetilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-hidroximetil-6-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3-dimetoxifenoxi)metil)carbonil-2,5-

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dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-(metoxicarbonil)-5-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-metoxi-4-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dimetoxi-4-(prop-3-enil)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((2-acetil-5-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-acetil-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-acetil-3-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,6-dimetoxi-4-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-di(*t*-butil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2,4-di(*t*-butil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3,5-di(*t*-butil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-di(isopropil)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

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(trans)-1-((2-metoxi-4-(etoxicarbony)metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-etoxi-5-prop-2-enilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-5-prop-2-enilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans) -1-((2,6-di(1-metilpropil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,4-difluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-difenilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-nitro-3-trifluorometilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-ciclopentyfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-ciclopentilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,3-difluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-6-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-amino-4-cloro-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3,4-difluorofenoxi)metil)carbonil-2,5-

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dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-carboxi-6-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,4-dicarboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,3-dimetoxi-5-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-bromo-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2,6-dichoro-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-metil-4-isopropilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((fluoren-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-dietilaminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-amino-3-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((2-oxo-3,4,8-trimetil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-acetil-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-fluoro-4-bromofenoxi)metil)carbonil-2,5-

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dımetil-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-(metılcarbonıl)amıno-5-metilfenoxı)metıl) carbonil-2,5-dimetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-(((1-acetilnaftalen-2-ıl)oxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-metoxı-4-nıtrofenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(trans)-1-((3-metil-5-ısopropılfenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2-metıl-4-formilfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-(((1-aminonaftalen-2-ıl)oxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) piperazina;

(trans)-1-((4-amınonaftalen-1-il)oxı)metıl)carbonıl-2,5-dimetil-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2-metoxı-4-(1,2-dıhıdroxıetıl)fenoxı)metıl) carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-(((3-(2-amınoetıl)ındolın-5-ıl)oxi)metıl)carbonıl-2,5-dımetil-4-(4- fluorobencil)piperazına,

(trans)-1-(((5-cloroquinolin-8-ıl)oxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-metoxi-4-(2-(amino)etıl)fenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(trans)-1-((4-(2-(amıno)etıl)fenoxı)metil)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

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(trans)-1-((2-metoxı-4-(2-(amıno)etıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2,4-diaminofenoxi)metil)carbonıl-2,5-dımetil-4-(4-fluorobencil)piperazına;

(trans)-1-((4-amınofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2-(dıetılamıno)metıl-4-amınofenoxı)metıl) carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-metıl-5-(2-amınobutıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2-(benzotriazol-2-il)-4-(1,1,3,3-tetrametıl-butıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2-nıtro-4-bromo-6-fluorofenoxı)metıl)carbonıl-2,5- dımetıl-4-(4-fluorobencıl)piperazına;

(trans)-1-((2-ıodofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazına;

(trans)-1-((2-(2-carboxietıl)fenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencil)piperazına;

(trans)-1-((2-carboxı-4-metilfenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)piperazina;

(trans)-1-((2,6-dibromo-3-carboxifenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2,6-dıcloro-3-carboxıfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazına;

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(trans)-1-((2-metoxi-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2,6-dimetoxi-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(2-carboxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-(2-hidroxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3-(2-hidroxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(2-hidroxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-(2-hidroxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2,4-dibromo-6-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-fluoro-6-formilfenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2,4-dicloro-6-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2,4-diiodo-6-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-6-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-etoxi-6-formilfenoxi)metil)carbonil-2,5-

dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-formil-5-(dietilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-formil-5-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-formil-3,5-dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-formil-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-formil-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-(((4-metoxinaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-5,6-dimetoxifenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-nitro-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((fluoren-9-on-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((4-hidroxi-1,2,3,4-tetrahidronaftalen-8-il) oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3,4,5,6-pentabromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-metil-3,4,5,6-tetrabromofenoxi)metil)car-

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bonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2,3,4-triclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-metil-4-bromo-6-clorofenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2-cloro-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2,4,6-triiodofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-formil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((1-bromonaftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((1,6-dibromonaftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((1-nitrosonaftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2,4-dicloronaftalen-1-il)oxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((2-nitronaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-(((2-carboxinaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-metilnaftalen-1-il)oxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(trans)-1-(((3-(hidroxisulfonil)-7-(dimetilamino)naftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((4-metoxinaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((1-formilnaftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((1-carboxinaftalen-1-il)oxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((1-amino-4-(hidroxisulfonil)naftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(naftalen-2-il)aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((3-aminonaftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-fluoro-4-(carboximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-cloro-4-(carboximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-(carboximetil)fenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(trans)-1-((4-hidroximetilfenoxi)metil)carbonil-2,5-

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dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-(hidroximetil)-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2,6-di(hidroximetil)-4-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-mercaptofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((2-carboxiindol-5-il)oxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-(((3-carboxiindol-5-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((indol-4-il)oxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-(((indol-5-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(benzoxazol-2-il)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina,

(trans)-1-(((2-metilquinolin-8-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((5,7-dibromoquinolin-8-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((5,7-diiodoquinolin-8-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

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(trans)-1-(((5-nitroquinolin-8-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((quinolin-5-il)oxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-(((5-(hidroxisulfonil)-7-iodoquinolin-8-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-(((2-fenil-4-oxo-4*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-2,5,7,8-tetrametil-2,3-dihidro-1-benzopiran-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((2-oxo-3-cloro-4-metil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((2-oxo-3-(dietilamino)metil)-4-metil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-oxo-6-metoxi-2*H*-1-benzopiran-7-il)oxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-oxo-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-metoxi-4-formil-6-bromofenoxi)metil)carbo-

nıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2-metoxı-4-formıl-6-ıodofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)piperazına;

(trans)-1-((2-metoxi-4-formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına,

(trans)-1-((2-etoxı-4-formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-carboxı-4-formılfenox)metil)carbonıl-2,5-dimetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2,4-dıcloro-6-nıtrofenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2,4-dınıtro-6-formılfenoxı)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)piperazina;

(trans)-1-((2,4-dinitro-6-carboxıfenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencıl) piperazına;

(trans)-1-((2,4-dınıtro-6-metılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazina,

(trans)-1-((2,5-dınıtrofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-nıtro-5-metılfenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazina;

(trans)-1-((2-nıtro-4-clorofenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2,4-dınıtrofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

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(trans)-1-((2-nitro-4-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-nitro-4-formil-6-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-nitro-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-nitro-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dinitro-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-nitro-4-(carboximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,6-diclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-metoxi-5-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(1-metil-1-feniletil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-(etilamino)-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-(((2-acetilnaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(carboximetil)fenoxi)metil)carbonil-2,5-

dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((4-(carboxımetıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil) piperazına;

(trans)-1-(((benzotrıazol-1-ıl)oxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-(((quınolın-2-ıl)oxı)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((4-formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2,6-dımetoxı-4-formılfenoxı)metıl)carbonıl-2,5- dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((3,4-dımetoxıfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2,4,6-trı(t-butıl)fenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2,6-dımetoxi-4-(metoxıcarbonıl)fenoxı)metıl) carbonıl-2,5-dımetıl-4-(4-fluorobencıl)piperazina;

(trans)-1-((3-trifluorometoxifenoxı)metıl)carbonıl-2,5-dımetıl-4- (4-fluorobencıl)piperazına,

(trans)-1-((2-metıl-5-amınofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)piperazina,

(trans)-1-((4-(4-cıanofenıl)fenoxı)metil)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(trans)-1-((3-nitro-4-amınofenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl) pıperazına,

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(trans)-1-((3-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-metilfenox)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(metoxicarbonil)metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((carbazol-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-(((2-oxo-1,3-benzotiol-2-on-6-il)oxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-(((2-fenil-4-oxo-4*H*-1-benzopiran-3-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((2-oxo-4-metil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-carboxi-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-metoxi-5-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((2-fenil-4-oxo-2,3-dihidro-4*H*-1-benzopiran-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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(trans)-1-(((quinolin-6-il)oxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,3-diaminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(hidroxisulfonil)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-(((fluorenon-9-on-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((5,6,7,8-tetrahidronaftalen-1-il)oxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((5,6,7,8-tetrahidronaftalen-2-il)oxi)metil) carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-9-((2,4,6-tribromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dibromo-4-cianofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3,5,6-tetrafluorofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-difluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3-diclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3,6-triclorofenoxi)metil)carbonil-2,5-

dimetil-4-(4-fluorobencil) piperazina

(trans)-1-((2-cloro-4,5-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,5-diclorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-cloro-5-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(metilcarbonil)aminofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((2-isopropoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-(benciloxi)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-etoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-fenilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2-(etoxicarbonil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-(etilcarbonil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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(trans)-1-((2-(*t*-butil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-isopropilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-(1-metilpropil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,3,5-trimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,3,6-trimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((2,4-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2,4,6-trimetoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metil-5-isopropilfenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina,

(trans)-1-((2,5- dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,5-dimetil-4-(dietilamino)metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-(*t*-butil)-6-metilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-prop-3-enil-6-metilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-prop-2-enilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-etilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-*n*-propilfenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina,

(trans)-1-((3-fluorofenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,5-difluorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3-cloro-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,5-diclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-iodofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-(fenilamino)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-(dietilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3-fenilfenoxi)metil)carbonil-2,5-dimetil-4-

(4-fluorobencil)piperazina,

(trans)-1-((3-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-trifluorometilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-*t*-butilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3-isopropilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-metil-4-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3,4-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-*t*-butil-5-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-isopropil-5-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3-etilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dimetil-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,6-dibromo-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-bromo-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

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(trans)-1-((2-metil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-isopropil-4-cloro-5-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(metilcarbonil)aminofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-etoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-propoxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((4-*n*-butoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-*n*-hexoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-*n*-heptoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-(propoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(etilcarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-(1,1,3,3-tetrametilbutil)fenoxi) metil) carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(trans -1-((4-(1,1-dimetilpropil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-(1-metilpropil)fenoxi)metil)carbonil-2,5-

dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-acetil-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-(*t*-butil)-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-(etilamino)-4-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(metoxicarbonil)metilfenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((4-etilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-*n*-propilfenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina,

(trans)-1-((2-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4,6-dibromofenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4,6-diclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4,6-diiodofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-6-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-carboxi-6-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-5-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-carboxi-5-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-5-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-carboxi-4-bromofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-carboxi-4- clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-carboxi-4-iodofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2- carboxi-4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-clorofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3,4-triclorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2,3,4,5,6-pentaclorofenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,4,5-triclorofenoxi)metil)carbonil-2,5-

dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((3-metoxifenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((3-(etoxicarbonil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2,6-dimetil-4- bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,5-dimetil-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-metil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-isopropil-4-cloro-5-metilfenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-etoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-(*t*-butil)-4- metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-formil-4-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-prop-3-fenilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-(1-feniletil)-4-clorofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((4-(etoxıcarbonil)metilfenoxı)metıl) carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((4-trıfluorometoxıfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına,

(trans)-1-((3-fluoro-4- clorofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-fluoro-4-clorofenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-(((7- metoxınaftalen-2-ıl)oxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((2-bencıloxı-4-cıanofenoxı)metıl) carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2-cloro-3,5-dımetoxıfenoxı)metil)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-bromo-3,5- dımetoxıfenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencil) pıperazına;

(trans)-1-((3,5-dımetoxi-4-bromofenoxi) metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dıbromo-3,5-dımetoxıfenoxı)metıl)carbonıl-2,5- dımetıl-4-(4-fluorobencıl)piperazina;

(trans)-1-((4- clorofenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencil)pıperazına;

(trans)-1-((3-nıtrofenoxı)metıl)carbonıl-2,5-dımetıl-4-

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(4-fluorobencil)piperazina,

(trans)-1-((2-metil-3- nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,5-dimetoxifenoxi)metil)carbonil-2, 5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2- nitro-3-carboxi-6-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3-cianofenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(trans)-1-((2-nitro-5- carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-(carboximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-5-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-(dimetilamino)metilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(2-(dimetilamino)etilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((naftalen-1-il)oxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((5-aminonaftalen-1-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((3-nitro-4-aminofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans-1-((2,6-di(*t*-butil)-4-metilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-carboxi-4-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-metil-5-carboxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-nitro-4-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((4-(benciloxi)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina,

(trans)-1-((3,5-di(trifluorometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2,4-dibromofenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dibromo-4-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,4-diclorofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-metoxifenoxi)metil)carbonil-2,5-dimetil-4-

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(4-fluorobencil) piperazina;

(trans)-1-((3,5-dimetil-4-bromofenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,5-dicarboxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-cloro-4- carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-dicloro-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((2-carboxiquinolin-4-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2,6-dimetil-4-formilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2,6-di(t-butil)-4-carboxifenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-amino-5-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2,6-di(t-butil)-4-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((4-carboxiquinolin-2-il)oxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3-nitro-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3-etil-4-cloro-5- metilfenoxi)metil)car-

bonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,5-di(metoxicarbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(morfolin-4-il)metil-4-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2- cloro-4-bromofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-trifluorometilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-metil-4-acetilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3-(dimetilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3-metil-4- acetilfénoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((3,5-dimetilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4- fenilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-(etoxicarbonil)fenoxi)metil)carbonil-2,5-

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dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((4- acetılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((4-bencılfenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2-metoxı-4- carboxıfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazına;

(trans)-1-(((3-carboxınaftalen-2-ıl)oxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2- (hıdroxımetıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-(((quınolın-8-ıl)oxı)metıl) carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazına,

(trans)-1-((3-amınofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(trans)-1-((4-(aminocarbonil)fenoxı)metıl) carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((3,5-dımetoxıfenoxı)metıl)carbonil-2,5-dimetıl-4-(4- fluorobencil)pıperazına;

(trans)-1-((2-(cıclohexıl) fenoxı)metıl)carbonil-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-(((quınolın-6-ıl)oxı)metıl)carbonıl-2,5-dımetıl-4- (4-fluorobencıl)pıperazına,

(trans)-1-((2,4-dıcloro-3-metılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)piperazina;

(trans)-1-((2, 5-dımetılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) piperazına;

(trans)-1-((3-bromofenoxı)metıl)carbonıl-2, 5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((3- (metilcarbonıl)amınofenoxı)metıl)carbonil-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((3-acetılfenoxı) metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına,

(trans)-1-((3-trıfluorometılfenoxı)metıl)carbonıl-2,5-dımetıl-4- (4-fluorobencıl)pıperazına,

(trans)-1-((4-bromofenoxı) metıl)carbonıl-2,5-dimetil-4-(4-fluorobencıl)piperazına;

(trans)-1-((2-formılfenoxı)metil)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(trans)-1-((2-metoxı-5- formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-(((tropınon-ıl)oxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencil)pıperazına;

(trans)-1-((2-nıtro-5-fluorofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-nitro-5-formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazına;

(trans)-1-((3-formıl-4-nıtrofenoxi)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencil) piperazina;

(trans)-1-((2-carboxı-5-nıtrofenoxı)metıl) carbonıl-2,5-

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dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2-amıno-4-nıtrofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencil)pıperazına;

(trans)-1-((2-amıno-3-carboxıfenoxi)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-nıtro-4-amınofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(trans)-1-((2,6- dıcloro-4-nıtrofenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencıl) pıperazına,

(trans)-1-((3-fluoro-4-nıtrofenoxı)metıl) carbonil-2,5-dımetıl-4-(4-fluorobencil)piperazina;

(trans)-1-((2,3-dıfluoro-6-nitrofenoxi)metil)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına,

(trans)-1-((2-cloro-4-nıtrofenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-nitro-4-cıanofenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(trans)-1-((2-bromo-4-metılfenoxi)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına,

(trans)-1-((3-clorofenoxı)metıl)carbonıl-2, 5-dımetıl-4-(4-fluorobencıl)pıperazına;

(trans)-1-((3,4-dıclorofenoxı)metıl)carbonıl-2, 5- dimetıl-4-(4-fluorobencıl)piperazına;

(trans)-1-((3,5-dıclorofenoxı)metıl)carbonil-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

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(trans)-1-((3,4,5-trimetilfenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-fluorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((3,5-dimetil-4-clorofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(metoxicarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-trifluorometilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-t-butilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((4-isopropilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-(((naftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((6-bromonaftalen-2-il)oxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(trans)-1-((3-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-metoxi-5-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((1,3-benzodioxolan-5-il)oxi)metil)carbonil-

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2,5- dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2,6-dimetil-4-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(trans)-1-((2-nitrofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-((2-metoxi-4-(amino)metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((3-(aminocarbonil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-ffluorobencil)piperazina;

(trans)-1-((3-(metoxicarbonil)metilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(4-fenilcarbonil)-4-fluorofenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(1-metil)ciclohexil-2,4-dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-(benciloxicarbanil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-(4-(metil)fenilcarbonil)-5-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-fenilcarbonil-5-octoxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((4-octilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

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(trans)-1-((2-(2-(carboxi)fenilcarbonil-5- di(*n*-butil) aminofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-fenilcarbonil-5- metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-metoxi-4-(3-hidroxiprop-2-enil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(trans)-1-(((3-(fenilaminocarbonil)naftalen-2-il)oxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-(((6-(fenilcarbonil)naftalen-2-il)oxi)metil) carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-((2-feniletil)carbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-((4-fluorofenil) carbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((2-(fenilamino)carbonilfenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((2-fenilcarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(trans)-1-((2-fenilcarbonil-4-cloro-5-metilfenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(trans)-1-((4-(4-clorofenil)carbonilfenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((4-bencilcarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(trans)-1-((2-fenilcarbonil-4- metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans)-1-((4-(2-metilcarboniletil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(trans) -1-((4-fenilcarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina; y

(trans)-1-((3- fenilcarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina

C. en forma similar, se prepararon los siguientes compuestos de fórmula (1b)

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(bencil)piperazina, RMN ($CDCl_3$) 7,6 (m, 3), 7,5 (m, 4), 6,2 (s, 2), 4,6 (m, 4), 4,2 (m, 4), 3,8 (m, 9), 3,4 (m, 1), 2,6 (m, 1) ppm;

1-((3- metoxifenoxi)metil)carbonil-4-(bencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 5), 6,5 (m, 4), 4,6 (s, 2), 3,8-3,5 (m, 9), 2. 4 (m, 4) ppm,

1-((3,4-dimetoxifenoxi)metil)carbonil-4-(bencil) piperazina; RMN ($CDCl_3$) 7,8 (m, 2), 7,4 (m, 3), 6,8 (d, 1), 6,6 (d, 1), 6,4 (dd, 1), 4,8 (d, 2), 4,3 (m, 3), 4,0 (m, 1), 3,7 (s, 3), 3,65 (s, 3), 3,6-3,3 (m, 8), 3,2-2,9 (m, 3) ppm,

1- ((fenoxi)metil)carbonil-4-(bencil)piperazina y 1-

(cloro)acetil-4- (bencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 7), 7,0 (m, 3) , 4,7 (s, 2), 3,6 (m, 6), 2,4 (m, 4) ppm;

1-((4-clorofenoxi) metil)carbonil-4-(bencil)piperazina y 1-(cloro)acetil-4-(bencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 7), 6,9 (m, 2), 4,6 (s, 2), 3,6 (m, 6), 2,4 (m, 4) ppm,

1-((3-cianofenoxi)metil) carbonil-4-(bencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (m, 4), 6,8 (m, 3), 4,4 (q, 2), 4,2 (d, 1), 3,9 (d, 2), 3,6 (m, 3), 3,0 (m, 3), 2,6 (m, 2) ppm,

1-((4-cianofenoxi)metil)carbonil-4- (bencil)piperazina; RMN ($CDCl_3$) 7,6 (m, 4), 7,4 (m, 3) , 7,0 (d, 2), 4,9 (q, 2), 4,6 (d, 1), 4,3 (d, 2), 4,0 (d, 2), 3,6 (t, 1), 3 4 (d, 2), 3,0 (m, 2) ppm;

1-((3-(1-metilimidazolin-2il) fenoxi)metil)carbonil-4-(bencil)piperazina; RMN ($CDCl_3$) 7,5 (m, 6), 7,2 (m, 3), 5,0 (d, 2), 4,0 (m, 4), 3,3 (q, 4), 3,0 (m, 6) ppm;

1-((4-cloro-2-aminocarbonilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina; RMN (DMSO-d_6) 8,7 (s, 1), 7. 8 (s, 1), 7,7 (s, 1), 7,6 (dd, 1), 7,4 (q, 3), 7,2 (d, 1), 5,0 (s, 2), 3. 4 (br d, 4), 3,3 (s, 2), 2,4 (br d, 4) ppm,

1-((5-cloroquinolin- 8-iloxi)metil)carbonil-4-(4-fluoro-

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bencil)piperazina; RMN (DMSO-d_6) 9,0 (s, 1), 8,5 (d, 1), 7,75 (dd, 1), 7,65 (d, 1), 7,4 (q, 2), 7,1 (d, 1), 5,1 (s, 2), 3,5 (m, 6), 2,4 (br d, 4) ppm;

1- ((3-trifluorometoxifenoxi)metil)carbonil-4-(bencil) piperazina,

1-(3-(3,4,5-trimetoxifenoxi)propil)carbonil-4-(bencil)piperazina;

1-(1-(3,4,5-trimetoxifenoxi)propil)carbonil-4-(bencil) piperazina;

1-(1-(3,4,5-trimetoxifenoxi)pentil)carbonil-4-(bencil) piperazina;

1-((4-metoxifenoxi)metil)carbonil-4-(bencil)piperazina;

1-((3,5-dimetoxifenoxi)metil)carbonil-4-(bencil)piperazina;

1-((3-clorofenoxi)metil)carbonil-4- (bencil)piperazina;

1-(1-(3,4,5-trimetoxifenoxi)etil)carbonil-4-(bencil) piperazina,

1-((3,4-diclorofenoxi)metil)carbonil-4-(bencil)piperazina,

1-((3,5-diclorofenoxi)metil)carbonil-4-(bencil)piperazina,

1-((3,4,5-trimetilfenoxi)metil)carbonil-4-(bencil)piperazina,

1-((4-nitrofenoxi)metil)carbonil-4-(bencil)piperazina;

1-(1-(3,4,5-trimetoxifenoxi)septil)carbonil-4- (bencil)

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piperazina,

1-(1-(3,4,5-trimetoxifenoxi)-2- metilpropil)carbonil-4-(bencil)piperazina;

1-(1-(3,4,5-trimetoxifenoxi)butil)carbonil-4-(bencil)piperazina;

1-((4-bromofenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-fluorofenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-trifluorometilfenoxi)metil)carbonil-4-(bencil)piperazina,

1-(((4-clorofenil)tio)metil)carbonil-4-(bencil)piperazina;

1-((2-clorofenoxi)metil)carbonil-4-(bencil)piperazina,

1-((4-(benciloxi)fenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-(metoxicarbonil)fenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-(amino)fenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-hidroxifenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-(1-metiletil)fenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-(2,2-dimetiletil)fenoxi)metil)carbonil-4- (bencil) piperazina,

1-((4-(acetil)fenoxi)metil)carbonil-4-(bencil)piperazina,

1-((naftalenil-2-oxi)metil)carbonil-4-

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(bencil)piperazına;

1-((4-cloro-3,5-dımetılfenoxı)metıl)carbonıl-4-(bencıl)pıperazına;

1-((1,3-benzodıoxolıl-5-oxı)metıl)carbonıl-4-(bencıl)pıperazına;

1-((2,4,6-trıclorofenoxı)metıl)carbonıl-4-(bencıl)pıperazına;

1-((2,3,4,5,6-pentafluorofenoxi)metıl)carbonıl-4-(bencıl)pıperazına;

1-((2-(bencıloxı)-4-cıanofenoxı)metıl)carbonıl-4-(bencıl)pıperazına;

1-((2-cloro-4-bromofenoxı)metıl)carbonil-4-(bencil) pıperazına,

1-((3-bromofenoxı)metıl)carbonıl-4-(bencil)pıperazina;

1-((3,5-trifluorometılfenoxı)metıl)carbonıl-4-(bencıl)pıperazına;

1-(((5-oxo-6,7,8-trihidronaftalen-1-il)oxı)metil)carbonil-4-(bencil) piperazina;

1-(((2-oxo-2*H*-1-benzopıran-4-il)oxi)metil) carbonil-4-(bencıl)pıperazına,

1-((2-cıanofenoxi)metil) carbonil-4-(bencil)pıperazina;

1-((4-metıl-3,5-dıbromofenoxi) metil)carbonıl-4-(bencıl)pıperazına,

1-((quınolınıl-6-oxı)metıl)carbonıl-4-(bencıl)pıperazına,

1-(((difenil)metoxi)metil)carbonil-4-(bencil)piperazina;

1-((3-(morfolin-4-il)fenoxi)metil)carbonil-4-(bencil)piperazina;

1-((2-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina, sal clorhidrato;

1-((piridinil-3-oxi)metil)carbonil-4-(bencil)piperazina;

1-((2-(bencil)fenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-(bencil)fenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-(formil)fenoxi)metil)carbonil-4-(bencil)piperazina,

1-((2-(prop-3-enil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dibromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((benzotiazolil-2-oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-ciclohexilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(benciloxi)carbonilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((5-cloroquinolinil-8-oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(imidazol-1-il)fenoxi)metil)carbonil-4-(4-

clorobencil)piperazina;

1-((3-cloro-5-metoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-carboxifenoxi)metil)carbonil-4-(bencil)piperazina;

1-((4-iodofenoxi)metil)carbonil-4-(4-cloro-bencil)piperazina, sal clorhidrato; RMN (DMSO-d_6) 7,6 (m, 6), 6,8 (d, 2), 4,9 (d, 2), 4,4 (m, 3), 4,0 (m, 1), 3,6 (m, 1), 3,4-2,9 (m, 6) ppm;

1-((2-metoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,6-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metilquinolinil-4-oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2,3-dihidro-1*H*-inden-5-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((coumarin-4-iloxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-clorobeniloxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((4-clorofenil)amino)metil)carbonil-4-(4-clorobencil) piperazina, sal clorhidrato; RMN (DMSO-d_6) 11,4 (br s, 1), 7,6 (dd, 4), 7,1 (d, 2), 6,6 (d, 2), 4,4 (m, 4), 4,0 (m, 4), 3. 6-2,9 (m, 4) ppm;

1-((4-cloronaftalenil-1-oxi)metil)carbonil-4-(4-

clorobencil)piperazina,

1-(((4-clorofenil)(metil)amino)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((di(4-cloro)fenil)metoxi)metil)carbonil-4-(clorobencil)piperazina;

1-((3,5-dimetoxi-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina, RMN ($CDCl_3$) 7,2 (q, 4), 6,2 (s, 2), 4,7 (s, 2), 3,9 (s, 6), 3,6 (m, 4), 3,5 (s, 2), 2,4 (m, 4) ppm;

1-((5,7-dicloroquinolinil-8-oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((6-hidroxicumarin-4-iloxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-fluoro-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina, sal clorhidrato; RMN (DMSO- d_6) 11,8 (s, 1), 7,5 (m, 5), 7,1 (d, 1), 6,8 (d, 1), 5,0 (q, 2) , 4,3 (m, 3), 3,9 (m, 1), 3,6-2,9 (m, 6) ppm;

1-((2-(hidroximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-dibromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,4-diclorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-cloro-3-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina, RMN (DMSO-d_6) 7,6 (m, 6), 7. 3 (d, 1), 5,0 (q, 2), 4,3 (m, 3), 3,9 (m, 1), 3,5-2,9 (m, 6) ppm;

1-((4-bromo-2-formilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina, RMN (DMSO-d_6) 11,4 (br s, 1), 7,8 (m, 2), 7,5 (m, 4), 7,2 (d, 1), 5,2 (q, 2), 4,4 (m, 3), 4,0 (m, 1), 3,6-2,9 (m, 6) ppm;

1-((2-metoxi-5-nitrofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((4-metilfenoxi)metil)carbonil-4-(4- clorobencil) piperazina;

1-((4-bromo-2-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina, sal clorhidrato;

1-((2-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina sal clorhidrato;

1-((3,5-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina, sal clorhidrato;

1-((2-aminocarbonil-4-clorofenoxi)metil)carbonil-4-(4-fluorobencil)piperazina; RMN (DMSO- d_6) 8,7 (br s, 1), 7,8 (s, 1), 7,7 (s, 1), 7,6 (dd, 1) , 7,2 (m, 3), 7,2 (d, 1), 5,0 (s, 2), 3,5 (m, 6), 2,4 (m, 4) ppm;

1-((3,5-dimetoxi-4-bromofenoxi)metil)carbonil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 4),

6,2 (s, 2), 4,7 (s, 2), 3,9 (s, 6), 3,6 (m, 4), 3,5(s, 2), 2,4 (m, 4) ppm;

1-((3-formil-4-nitrofenoxi)metil)carbonil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10,5 (s, 1), 8,2 (d, 1), 7,3 (m, 6), 4,9 (s, 2), 3,6 (m, 2), -3,5 (m, 4), 2,4 (m, 4) ppm;

1-((2-cloro-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((1-nitroso-3,6-di(hidroxisulfonil)naftalen-2-iloxi)metil)carbonil-4- (4-clorobencil)piperazina;

1-((2-nitroso-4-hidroxisulfonilnaftalen-1-iloxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3,6-di(hidroxisulfonil)naftalen-1-iloxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-hidroxisulfonil-6-aminonaftalen-1-iloxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-hidroxisulfonil-7-aminonaftalen-1-iloxi)metil)carbonil- 4-(4-clorobencil)piperazina;

1-((5-hidroxisulfonilquinolin-8-iloxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3-dinitro-7-hidroxisulfonilnaftalen-1-iloxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2-carboxi-4-hidroxisulfonilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-4-hidroxisulfonilfenoxi)metil)carbonil-4-(4-

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clorobencil)piperazina;

1-((4-formil-2,6-di-t-butilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(morfolin-4-il)metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(metoxicarbonil)-2,6-diclorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-(hidroxisulfonil)naftalen-1-iloxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,6-di(hidoxisulfonil)-8-aminonaftalen-1-iloxi)metil) carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-5-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-trifluorometil-2,3,5,6,-tetrafluorofenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2-metoxi-4-formil-5-(2-hidroxi-3-metoxi-5-formilfenil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-carboxi-2,3,5,6-tetrafluorofenoxi)metil) carbonil-4-(4-clorobencil)piperazina;

1-((4-(adamant-1-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(adamant-1-il)-4-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,4-di((1-metil-1-fenil)etil)fenoxi)metil) carbonil-

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4-(4-clorobencil)piperazina;

1-((2-acetil-4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-*t*-butilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-acetil-4-cloro-5-metilfenoxi)metil) carbonil-4-(4-clorobencil)piperazina;

1-((2-acetil-4-cloro-6- nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-acetil-4,6-dibromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-formil-4,6-di(*t*-butil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dinitrofenoxi)metil)carbonil- 4-(4-clorobencil)piperazina,

1-((2,6-dicloro-4-etoxicarbonilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-etoxicarbonil-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-6-(prop-3-enil)fenoxi) metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-fluoro-4-cianofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-acetil-4-metil-6-nitrofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

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1-((2-metilbenzotiazol-5-iloxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-4-(hidroxisulfonil) fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(4-(trifluorometil)fenoxi)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-(1*H*-pirazol-3-il)-4-cloro-5-metilfenoxi)metil) carbonil-4-(4-clorobencil)piperazina;

1- ((2-(1*H*-pirazol-3-il)-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-fenil-4-oxo-7-hidroxi-4*H*-1-benzopiran-3-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-3-trifluorometilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-(butoximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((6-hidroxiquinolin-2-iloxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxicarbonil-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1- ((2,5-di(*t*-butil)-4-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-formil-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(2*H*-benzotriazol-2-il)-4-(2-hidroxietil)feno-

xi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(metiltio)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-di(t-butil) -4-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dibromo-4-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,6-diiodo-4-formilfenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2-nitro-4-metoxicarbonilfenoxi) metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(etoxicarbonil)indol-5-iloxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((3-(2-carboxietil)fenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2,6-dinitro-4-(carboximetil) fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-3-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((6-carboxinaftalen-2-iloxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,6-difluoro-4-etilcarbonilfenoxi)metil) carbonil-4-(4-clorobencil)piperazina;

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1-((2-(2-(metoxicarbonil) etil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(prop-3-enil)-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-(((3-oxo-2*H*-benzofuran-6-il)oxi)metil) carbonil-4-(4-clorobencil)piperazina,

1-((2,4,6-tribromo-3,5- dimetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(heptilcarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-nitro-4-fenilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-(eth-2-enil)fenoxi)metil)carbonil-4-(4-clorobenril)piperazina,

1-((2-cloro-4- metoxicarbonilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-diiodo-4-cianofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,6-diiodo-4-carboxifenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-(((2-fenil-4-oxo-4*H*-1-benzopiran-5-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((2-fenil-4-oxo-7-metoxi-4*H*-1-benzopiran-5-il) oxi)

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metil)carbonil-4-(4-clorobencil)piperazina,

1-(((2-fenil-4-oxo-7-metoxi-2,3-dihidro-4*H*-1-benzopiran-5-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-octilcarbonilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((4-ftalimid-1-ilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-(morfolin-4-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-cloro-4-bromofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-(((2-oxo-7-metoxi-2*H*-1-benzopiran-8-il)oxi)metil) carbonil-4-(4-clorobencil)piperazina,

1-((2-acetil-5-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1- ((2-(1-metilciclohex-1-il)-4-metil-6-(2-hidroxi-3-(1-metilciclohex-1-il)-5-metilbencil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-formil-3-metoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-amino-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-4-carboxi-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetil-4-carboxifenoxi)metil)carbonil-4-(4-

clorobencil)piperazina,

1- ((2-metoxi-4-(2-(carboxi)etil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,6-dimetoxi-4-(hidroximetil)fenoxi)metil) carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dibromo-4-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1- ((2-nitro-4-(etoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-amino-4-(metoxicarbonilo)fenoxi)metilo)carbonil-4-(4-clorobencil)piperazina;

1-((4-(2-(4-nitrofenil)et-2-fenil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-acetil-3,5-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,6-di(*t*-butil)-4-(metoxicarbonil)fenoxi)metil) carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-(etoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-ciclohexil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-etilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-((4-*n*-butilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((3-carboxi-1-bromonaftalen-2-il)oxi)metil)carbonil-4-(4- clorobencil)piperazina,

1-((2-bromo-4-nitro-6-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-formil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,6-dicloro-4-(etoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((4-metil-2-oxo-2*H*-1-benzopiran-6-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3-dibromo-4-formil-6-metoxifenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((4-(2-(4-nitrofenil)eth-2-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,4,6- tribromo-3-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-bencil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-(bezotiazol-2-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-nitro-6-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-etoxi-4-metilfenoxi)metil)carbonil-4-(4-

clorobencil)piperazina;

1- ((2-bromo-4,6-di(*t*-butil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-(pirrolidin-1-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(morfolin-4-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(piperidin-1-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2- formil-4-cloro-6-bromofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-(((4,7-dimetoxi-5-formilbenzofuran-6-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-oxo-4-metil-8-nitro-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2-metoxi-4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-4-bromo-6-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1- ((2,4-dimetil-6-*t*-butilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-(((2-nitro-4-(hidroxisulfonil)naftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((3-(hidroxisulfonil)-6-aminonaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-(((3-(hidroxisulfonil)-7-aminonaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((3-(metoxicarbonil)naftalen-2-il)oxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2-carboxi-4-(hidroxisulfonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-*n*-butilcarbonilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-etoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((4-(((2-etil)hexoxi)carbonil)fenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((4-((*n*-pentoxi)carbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-5-(metoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,4,6-tribromo-3-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-metoxi-4-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(2-(fenil)eth-2-enil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((4-(1,2,4-triazol-1-il)fenoxi)metil)carbonil-4-(4-

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clorobencil)piperazina,

1-((2-nitro-4-cloro-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(*n*-hexoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-cloro-4-formil-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-(2-(etoxicarbonil)etil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3,4,6-tetraclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-((2-metilpropoxi)carbonil)fenoxi)metil)carbonil-4-(4- clorobencil)piperazina,

1-((2-(*n*-butoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(fenilamino)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-hidroximetil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-mercaptofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-nitro-6-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,4-di(1-metilbutil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

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1-((3- trifluorometil-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,6-dibromo-4-(metoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-dicloro-6-acetil)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxicarbonil-4-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-formil-4-bromo-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-diformil-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dinitro-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-nitro-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-formil-4-nitro-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(aminocarbonil)metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxicarbonil-4-metoxifenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-(((2-fenil-4-oxo-4*H*-1-benzopiran-6-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-cloro-4-trifluorometilfenoxi)metil)carbonil-4-(4-

clorobencil)piperazina;

1-((2-carboxi-3-metil-6-isopropilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((5,7-dibromo-2-metilquinolin-8-il)oxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-(((5,7-dicloro-2-metilquinolin-8-il) oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dinitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-4-(1,1-dimetilpropil)fenoxi)metil)carbonil-4-(4- clorobencil)piperazina,

1-((2,6-Bifenil-4-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-dicloro-3-metil- 6-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((2-oxo-4-(carboxi)metil-2*H*-1-benzopiran-7-il)oxi)metil) carbonil-4-(4-clorobencil)piperazina;

1-(((2-oxo-4-trifluorometil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4- clorobencil)pipe-razina,

1-((2-*t*-butil-4-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-formil-6-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1- ((2-metoxıcarbonıl-4-acetilfenoxi)metil)carbonil-4-(4-clorobencıl) pıperazına;

1-((2-bromo-5-fluorofenoxı)metıl)carbonil-4-(4-clorobencıl)pıperazına;

1-((2,4-dı(1,1-dımetılpropıl)fenoxı)metıl)carbonıl-4-(4-clorobencil)piperazına;

1-((3-metıl-4-fluorofenoxı)metıl)carbonıl-4-(4-clorobencil)piperazına,

1-((2,3,4-trıfluorofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2,5-dıfluorofenoxi)metıl)carbonil-4-(4-clorobencıl) pıperazına;

1-((2-metıl-5-nıtrofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-(((2-metil-3-(etoxıcarbonıl)ındol-5-ıl)oxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-amınocarbonıl-4-acetılfenoxı)metıl)carbonıl-4-(4-clorobencil) pıperazına;

1-((2,6-dınitro-3-*t*-butılfenoxı)metıl)carbonıl-4-(4-clorobencil)pıperazına,

1-((2-fluoro-4-nıtrofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-carboxı-3-fluorofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-(2-etılhexoxı)carbonilfenoxi)metil)carbonil-4-(4-

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clorobencil)piperazina,

1-((2,4,6-tribromo-4-carboxifenoxi) metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(4-bromofenil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-(4-carboxifeny)fenoxi)metil)carbanil-4-(4-clorobencil)piperazina,

1-((2,3,6-trifluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,4,5-trifluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,4,6-trifluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-fluoro-5-trifluorometilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2,4-dinitronaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((3,6-di(hidroxisulfonil)-8-aminonaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-acetil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetil-4-(1-(3,5-dimetil-4-hidoxifenil)-1-metiletil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(3-(4-hidroxifenil)hex-2-il)fenoxi)metil)carbonil-

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4-(4-clorobencil)piperazina;

1-(((6-(hidroxisulfonil)naftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-cloro-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-bromo-4,5-difluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-cloro-4-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(2-(metoxicarbonil)etil)fenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2,6-difenil-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-3-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metil-4-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina

1-((2-metil-4-iodofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-fluoro-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-3-isopropil-6-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-((2-carboxı-3,4,6-trıclorofenoxı)metıl)carbonıl-4-(4-clorobencıl) pıperazına;

1-((2-carboxı-6-ısopropılfenoxi)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-(pıperıdın-1-ıl)-4- metılfenoxı)metıl)carbonıl-4-(4-clorobencıl)piperazına;

1-(((2,3-dıhıdro-2,2-dımetılbenzofuran-7-ıl)oxı)metıl)carbonıl-4-(4- clorobencıl)pıperazına;

1-((2,6-dı(t-butıl)-4-(1-metılpropıl)fenoxi)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((3-metıl-4-bromofenoxı)metıl)carbonıl-4-(4-clorobencil) pıperazına;

1-(((fenanthren-9-ıl)oxı)metıl)carbonıl-4-(4-clorobencıl) pıperazına;

1-((2-nıtro-4-bromofenoxı)metıl)carbonıl-4-(4-clorobencil)pıperazına;

1-((2-fluoro-3-trıfluorometılfenoxı)metıl)carbonıl-4-(4-clorobencıl)piperazına;

1-((2-nıtro-5-metoxıfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-cloro-4-amınofenoxı)metıl)carbonıl-4-(4-clorobencil)pıperazina;

1-((2-formıl-4-bromo-6-nıtrofenoxı)metıl)carbonıl-4-(4-clorobencil)pıperazına;

1-((2-metoxi-4-(acetil)metılfenoxi) metıl)carbonil-4-(4-

clorobencil)piperazina;

1-((4-(5- mercaptotetrazol-1-il)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,4,6-triiodo-3-(2-carboxi)butilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-hidroximetil-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3,5,6-tetrafluoro-4-(2,3,4,5,6-pentafluorofenil) fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(benzotriazol-2-il)-4,6-di(1,1-dimetilpropil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-fenil-3-hidroxi-4-oxo-4*H*-1-benzopiran-6-il)oxi) metil)carbonil-4-(4-clorobencil)piperazina;

1-((indanonil)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-(hidroxisulfonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-3-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-(2,4-dinitrofenil)aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-metil-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dibromo-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-((2,6-diiodo-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-formil-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-5-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-amino-4-*t*-butilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metil-3-aminofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-carboxi-5-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-metil-4-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,5-dimetil-4-aminofenoxi)metil)carbonil-4-(4-

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clorobencil)piperazına,

1-((2,6-dıbromo-4-amınofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-carboxı-4-amınofenoxı)metıl)carbonıl-4-(4-clorobencıl) pıperazına,

1-((2-amınocarbonılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-aminocarbonil-4-clorofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((4-(2-amınoetıl)fenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2,4,6-trı(dımetılamıno)fenoxı)metıl)carbonıl-4-(4-clorobencıl) pıperazına;

1-((2-hıdroxımetıl-6-metoxıfenoxı)metıl)carbonil- 4-(4-clorobencıl)pıperazına;

1-((2,3-dımetoxıfenoxi)metıl)carbonıl-4-(4-clorobencil)pıperazına,

1-((4-(metoxicarbonil)-5-metoxıfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1- ((2-metoxı-4-(metoxıcarbonıl)fenoxı)metıl)carbonil-4-(4-clorobencıl) pıperazına;

1-((2,6-dımetoxi-4-(prop-3-enil)fenoxı)metıl)carbonıl-4-(4-clorobencıl)piperazına;

1-((2-acetıl-5-metoxıfenoxı)metıl)carbonıl-4-(4-clorobencıl)piperazına,

1-((2-acetil-4-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-acetil-3-metoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-metoxi-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetoxi-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-di(*t*-butil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-di(*t*-butil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3,5-di(*t*-butil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-di(isopropil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-(etoxicarbony)metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-etoxi-5-prop-2-enilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-5-prop-2-enilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-di(1-metilpropil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-difluorofenoxi)metil)carbonil-4-(4-

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clorobencil)piperazina;

1-((2,6-difenilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-nitro-3-trifluorometilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-ciclopentyfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-ciclopentilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,3-difluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-carboxi-6-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-4- cloro-5-nitrofenoxi)metil)carbonil-4-(4-clorobenci)piperazina,

1-((3,4-difluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-carboxi-6-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,4-dicarboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3-dimetoxi-5-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-bromo-4-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dıchoro-4-fluorofenoxı)metıl)carbonıl-4-(4-clorobencıl) pıperazına,

1-((3-metıl-4-ısopropılfenoxı)metıl)carbonıl-4-(4-clorobencıl)piperazına;

1-(((fluoren-2-il)oxi)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-dietilaminofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-amıno-3-nıtrofenoxı)metil)carbonıl-4-(4-clorobencıl)piperazına;

1-(((2-oxo-3,4,8-trımetıl-2*H*-1-benzopıran-7-ıl)oxı)metil)carbonıl- 4-(4-clorobencıl)pıperazına;

1-((2-acetil-4-fluorofenoxı)metil)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-fluoro-4-bromofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-(metılcarbonıl)amino-5-metilfenoxi)metil)carbonil-4-(4-clorobencıl) pıperazına,

1-(((1-acetılnaftalen-2-ıl)oxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-metoxı-4-nıtrofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((3-metıl-5-ısopropılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-metil-4-formılfenoxı)metıl)carbonıl-4-(4-

clorobencil)piperazina;

1-(((1-aminonaftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-aminonaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-4-(1,2-dihidroxietil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((3-(2-aminoetil)indalin-5-il)oxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-(((5-cloroquinolin-8-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-4-(2-(amino)etil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(2-(amino)etil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-(2-(amino)etil)fenoxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2,4-diaminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-aminofenoxi)metil)carbonil- -(4-clorobencil)piperazina,

1-((2-(dietilamino)metil-4-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2- metil-5-(2-aminobutil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-(benzotriazol-2-il)-4-(1,1,3,3-tetrametilbutil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-bromo-6-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-iodofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(2-carboxietilo)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1- ((2,6-dibromo-3-carboxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,6-dicloro-3-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetoxi-4-carboxifenoxilmetil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(2-carboxietil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(2-hidroxietil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((3-(2-hidroxietil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-((4-(2-hıdroxıetıl)fenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-metoxi-4-(2-hidroxıetıl)fenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2,4-dıbromo-6-formılfenoxı)metil)carbonil-4-(4-clorobencıl) pıperazına;

1-((2-fluoro-6-formılfenoxı)metil)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2,4-dıcloro-6-formılfenoxı)metıl)carbonıl-4-(4-clorobencil)pıperazına;

1-((2,4-dıiodo-6-formılfenoxı)metıl)carbonıl-4-(4-clorobencil)piperazina;

1-((2-metoxı-6-formılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-etoxı-6-formilfenoxı)metil)carbonıl-4-(4-clorobencilo) pıperazına,

1-((2-formıl-5-(dietılamıno)fenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-formil-5-metoxıfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-formıl-3,5-dımetoxıfenoxı)metıl)carbonil-4-(4-clorobencıl)pıperazına ,

1-((2-formıl-4-bromofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-formıl-4-metoxıfenoxı)metıl)carbonıl-4-(4-

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clorobencil) piperazina,

1-(((4-metoxınaftalen-1-ıl)oxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-carboxı-5,6-dımetoxıfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((3-nıtro-4-metoxıfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-(((fluoren-9-on-1-ıl)oxı)metıl)carbonıl-4-(4-clorobencil)piperazına;

1-(((4-hıdroxı-1,2,3,4-tetrahıdronaftalen-8-ıl)oxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2,3,4,5,6-pentabromofenoxı)metıl)carbonil-4-(4-clorobencıl)pıperazına;

1-((2-metıl-3,4,5,6-tetrabromofenoxı)metil)carbonil-4-(4-clorobencıl) pıperazına,

1-((2,3,4-trıclorofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-metıl-4-bromo-6-clorofenoxı)metıl)carbonıl-4-(4-clorobencil)piperazına,

1-((2-cloro-4-fluorofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2,4,6-trıodofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-formıl-4-clorofenoxı)metıl)carbonil-4-(4-clorobencıl) pıperazına;

1-((3-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((1-bromonaftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((1,6-dibromonaftalen- 2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((1- nitrosonaftalen-2-il)oxi)metilo)carbonil-4-(4-clorobencil)piperazina;

1-(((2,4-dicloronaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((2-nitronaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-carboxinaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((2-metilnaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((3-(hidroxisulfonil)-7-(dimetilamino)naftalen-1-il)oxi) metil)carbonil-4-(4-clorobencil)piperazina;

1-(((4-metoxinaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((1-formilnaftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((1-carboxinaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((1-amino-4-(hidroxisulfonil)naftalen-2-il)oxi)me-

til)carbonil-4-(4-clorobencil) piperazina;

1-((4-(naftalen-2-il)aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((3-aminonaftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-fluoro-4-(carboximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-4-(carboximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-4-(carboximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-hidroximetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(hidroximetil)-4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-di(hidroximetil)-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-4-(hidroximetil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-mercaptofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-carboxiindol-5-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((3-carboxiindol-5-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((indol-4-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((indol-5-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(benzoxazol-2-il)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((2-metilquinolin-8-il)oxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-(((5,7-dibromoquinolin-8-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((5,7-diiodoquinolin-8-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((5-nitroquinolin-8-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((quinolin-5-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((5-(hidroxisulfonil)-7-iodoquinolin-8-il)oxi)metil)carbonil- 4-(4-clorobencil)piperazina;

1-(((2-fenil-4-oxo-4*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-2,5,7,8-tetrametil-2,3-dihidro-1-benzopiran-6-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-oxo-3-cloro-4-metil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-(((2-oxo-3-(dietilamino)metil)-4-metil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-(((2-oxo-6-metoxi-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-oxo-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metoxi-4-formil-6-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-formil-6-iodofenoxi) metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-etoxi-4-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-4-formilfenox)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,4-dicloro-6-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-dinitro-6-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-dinitro-6-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina:

1-((2,4-dinitro-6-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

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1-((2,5-dinitrofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-nitro-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-dinitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-nitro-4-formilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-nitro-4-formil-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dinitro-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-nitro-4-(carboximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-diclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-metoxi-5-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-cianofenoxi)metil)carbonil-4-(4-

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clorobencil)piperazina;

1-((4-(1-metil-1-feniletil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-(etilamino)-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-acetilnaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(carboximetil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-(carboximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((benzotriazol-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((quinolin-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetoxi-4-formilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3,4-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,4,6-tri(*t*-butil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetoxi-4-(metoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-((3-trifluorometoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-metil-5-aminofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((4-(4-cianofenil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-nitro-4-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-metilfenox)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(metoxicarbonil)metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-(((carbazol-2-il)oxi)metil)carbonil-4-(4- clorobencil) piperazina;

1-(((2-oxo-1,3-benzotiol-2-on-6-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-fenil-4-oxo-4*H*-1-benzopiran-3-il)oxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-(((2-oxo-4-metil-2*H*-1-benzopiran-7-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-carboxi-4-aminofenoxi)metilo)carbonil-4-(4-

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clorobencil)piperazina;

1-((2-metoxi-5-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-fenil-4-oxo-2,3-dihidro-4*H*-1-benzopiran-6-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((quinolin-6-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3-diaminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(hidroxisulfonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((fluorenon-9-on-2-il)oxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-(((5,6,7,8-tetrahidronaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((5,6,7,8-tetrahidronaftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,4,6-tribromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-dibromo-4-cianofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3,5,6-tetrafluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-difluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3-diclorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,3,6-triclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-4,5-dimetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,5-diclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-cloro-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(metilcarbonil)aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-isopropoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(benciloxi)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-etoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-fenilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(metoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(etaxycarbonil)fenoxi)metil)carbonil-4-(4-

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clorobencil) piperazina;

1-((2-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(etilcarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(t-butil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-isopropilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(1-metilpropil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,3-dimetilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,3,5-trimetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,3,6-trimetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-dimetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,4,6-trimetoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metil-5-isopropilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,5-dimetilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

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1-((2,5-dımetıl-4-(dietilamino)metilfenoxı)metıl)carbonıl-4-(4-clorobencil)piperazina,

1-((2-(*t*-butil)-6-metilfenoxı)metıl)carbonil-4-(4-clorobencıl)pıperazına;

1-((2,6-dımetoxıfenoxi)metıl)carbonıl-4-(4-clorobencil)pıperazina,

1-((2-prop-3-enıl-6-metilfenoxı)metil)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-prop-2-enılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-etilfenoxi)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-*n*-propılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((3-fluorofenoxi)metil)carbonıl-4-(4-clorobencil)piperazına,

1-((3,5-difluorofenoxi)metıl)carbonıl-4-(4-clorobencıl)pı-perazina,

1-((3-cloro-4-fluorofenoxı)metıl)carbonıl-4-(4-clorobencıl) pıperazına,

1-((3,5-dıclorofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((3-ıodofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

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1-((3-(fenilamino)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3-(dietilamino)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-fenilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-trifluorometilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-t-butilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-isopropilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-metil-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,4-dimetilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-t-butil-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-isopropil-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-etilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-dimetil-4-bromofenoxi)metil)carbonil-4-(4-

clorobencil)piperazina;

1-((2,6-dibromo-4-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-bromo-4-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-metil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-isopropil-4-cloro-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(metilcarbonil)aminofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((4-etoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-propoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-*n*-butoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-*n*-hexoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-*n*-heptoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(propoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-(etilcarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

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1-((4-(1,1,3,3-tetrametilbutil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(1,1-dimetilpropil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(1-metilpropil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-metoxi-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-acetil-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(*t*-butil)-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-(etilamino)-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(metoxicarbonil)metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-etilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-*n*-propilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-4,6-dibromofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-carboxi-4,6-diclorofenoxi)metil)carbonil-4-(4-

clorobencil)piperazina;

1-((2-carboxi-4,6-diiodofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-6-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-6-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-5-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-carboxi-5-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-carboxi-5-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-carboxi-4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-carboxi-4-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-carboxi-4-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-carboxi-4-iodofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-carboxi-4-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3,4-triclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3,4,5,6-pentaclorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2,4,5-triclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-(metoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-(etoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dimetil-4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dimetil-4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-metil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1- ((2-isopropil-4-cloro-5-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-etoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-(*t*-butil)-4-metilfenoxi)metil)carbonil-4- (4- clo-

robencil)piperazina;

1-((3-formil-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-prop-3-enilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(1-fenyetil)-4-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((4-(etoxicarbonil)metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-trifluorometoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-fluoro-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-fluoro-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((7-metoxinaftalen-2-il)oxi)metil)carbonil-4-(4- clorobencil)piperazina;

1-((2-benciloxi-4-cianofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-3,5-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1- ((2-bromo-3,5-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3,5-dimetoxi-4-bromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-dibromo-3,5-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metil-3-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-nitro-3-carboxi-6-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-cianofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-5-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-5-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-(carboximetil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-metoxi-5-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(dimetilamino)metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(2-(dimetilamino)etilfenoxi)metil)carbonil-4-(4-

clorobencil)piperazina;

1-((3-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((naftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((5-aminonaftalen-1-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-nitro-4-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-di(t-butil)-4-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3-carboxi-4-nitrofenoxi)metil)carbonil-4-(4-lorobencil) piperazina,

1-((2-metil-5-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(benciloxi)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(aminocarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3,5-di(trifluorometil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,4-dibromofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dibromo-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,4-diclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dimetil-4-bromofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3,5-dicarboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-dicloro-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((2-carboxiquinolin-4-il)oxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2,6-dimetil-4-formilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-di(*t*-butil)-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-5-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,6-di(*t*-butil)-4-(hidroximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((4-carboxiquinolin-2-il)oxi)metil)carbonil-4-(4-

clorobencil)piperazina,

1-((3-nitro-4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-etil-4-cloro-5-metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((3,5-di(metoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(morfolin-4-il)metil-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina

1-((2-metoxi-4-cianofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-cloro-4-bromofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((2-trifluorometilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metil-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-(dimetilamino)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-metil-4-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dimetilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((4-fenilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(etoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-acetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-bencilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxi-4-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((3-carboxinaftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(hidroximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-(((quinolin-8-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-(aminocarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dimetoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-(ciclohexil)fenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-(((quinolin-6-il)oxi)metil)carbonil-4-(4- cloroben-

cıl)pıperazina;

1-((2,4-dıcloro-3-metılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2,5-dımetılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((3-bromofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((3-(metılcarbonıl)amınofenoxı)metıl)carbonıl-4-(4-clorobencil)piperazina;

1-((3-acetilfenoxı)metıl)carbonıl-4-(4-clorobencil)pıperazina;

1-((3-trifluorometilfenoxi)metıl)carbonil-4-(4-clorobencil)pıperazina;

1-((4-bromofenoxi)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-formilfenoxi)metil)carbonıl-4-(4-clorobencil)piperazina;

1-((2-metoxı-5-formılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-(((tropınon-ıl)oxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-nitro-5-fluorofenoxı)metil)carbonıl-4-(4-clorobencıl)pıperazina;

1-((2-nıtro-5-formılfenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((3-formil-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-carboxi-5-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-amino-3-carboxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-aminofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2,6-dicloro-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3-fluoro-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2,3-difluoro-6-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((2-cloro-4-nitrofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-nitro-4-cianofenoxi)metil)carbonil-4-(4-clorobencil) piperazina;

1-((2-bromo-4-metilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,4-diclorofenoxi)metil)carbonil-4-(4-

clorobencil)piperazina;

1-((3,5-diclorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((3,4,5-trimetilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-fluorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3,5-dimetil-4-clorofenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-((4-metoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-(metoxicarbonil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-trifluorometilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina,

1-((4-*t*-butilfenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((4-isopropilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina,

1-(((naftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-(((6-bromonaftalen-2-il)oxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((3-(hidroximetil)fenoxi)metil)carbonil-4-(4-clorobencil)piperazina;

1-((2-metoxı-5-(hidroxımetıl)fenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-(((1,3-benzodioxolan-5-il)oxı)metıl)carbonıl-4-(4-clorobencil)piperazina;

1-((2,6-dımetıl-4-nıtrofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazina,

1-((2-nıtrofenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazına,

1-((2-metoxı-4-(amıno)metılfenoxı)metıl)carbonıl-4-(4-clorobencıl) pıperazına;

1-((3-(amınocarbonıl)fenoxı)metıl)carbonıl-4-(4-clorobencıl)pıperazina,

1-((3-(metoxıcarbonil)metılfenoxi)metıl)carbonıl-4-(4-clorobencıl)pıperazına;

1-((2-(4-fenılcarbonıl)-4-fluorofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

1-((2-(1-metıl)cıclohexıl-2,4-dımetılfenoxı)metil)carbonil-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

1-((2-(bencıloxıcarbonıl)fenoxı)metıl)carbonıl-4-(4-fluorobencıl)pıperazına;

1-((2-(4-(metıl)fenılcarbonıl)-5-metoxıfenoxi)metıl) carbonıl-4-(4-fluorobencil)piperazına;

1-((2-fenılcarbonıl-5-octoxıfenoxı)metıl)carbonıl-4-(4-fluorobencıl) pıperazına;

1-((4-octılfenoxı)metıl)carbonıl-4-(4-

fluorobencil)piperazina;

1-((2-(2-(carboxi)fenilcarbonil-5-di(*n*-butil)aminofenoxi)metil)carbonil-4-(4-fluorobencil)piperazina;

1-((2-fenilcarbonil-5-metoxifenoxi)metil)carbonil-4-(4-fluorobencil) piperazina;

1-((2-metoxi-4-(3-hidroxiprop-2-enil)fenoxi)metil) carbonil-4-(4-fluorobencil)piperazina;

1-(((3-(fenilaminocarbonil)naftalen-2-il)oxi)metil)carbonil-4-(4- fluorobencil)piperazina,

1-(((6-(fenilcarbonil)naftalen-2-il)oxi)metil)carbonil-4-(4-fluorobencil)piperazina,

1-((2-((2-feniletil)carbonil)fenaxy)metil)carbonil-4-(4-fluorobencil)piperazina;

1-((4-((4-fluorofenil)carbonil)fenoxi)metil)carbonil-4-(4- fluorobencil)piperazina

1-((2-(fenilamino)carbonilfenoxi)metil)carbonil-4-(4-fluorobencil)piperazina;

1-((2-fenilcarbonilfenoxi)metil)carbonil-4-(4-fluorobencil)piperazina,

1-((2-fenilcarbonil-4-cloro-5-metilfenoxi)metil)carbonil-4-(4- fluorobencil)piperazina;

1-((4-(4-clorofenil)carbonilfenoxi)metil)carbonil-4-(4-fluorobencil)piperazina,

1-((4-bencilcarbonil)fenoxi)metil)carbonil-4-(4-fluorobencil)piperazina;

1-((2-fenilcarbonil-4-metilfenoxi)metil)carbonil-4-(4-fluorobencil)piperazina,

1-((4-(2-metilcarboniletil)fenoxi)metil)carbonil-4-(4-fluorobencil)piperazina;

1-((4-fenilcarbonilfenoxi)metil)carbonil-4-(4-fluorobencil)piperazina, y

1-((3-fenilcarbonilfenoxi)metil)carbonil-4-(4-fluorobencil) piperazina;

D. en forma similar se prepararon los siguientes compuestos de fórmula (Ia) o (Ib):

metiléster de ácido 5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico, ^{1}H RMN (400 MHz, DMSO-d_6): δ/ppm = 0,86-1,02 (m, 3H), 1,04-1,36 (m, 3H), 2,16 (m, 1H), 2,62 (m, 1H), 2,94 (m, 1H), 3,08 (m, 0,5H), 3,42 (m, 1H), 3,58 (m, 1H), 3,76 (s, 3H), 3,98 (m, 1H), 4,40 (s, 0,5H), 4,82 (m, 1,5H), 5,02 (m, 0,5H), 6,98 (s, 1H), 7,14 (m, 2H), 7,38 (m, 2H), 7,56 (m, 1H), 7,62 (s, 1H).

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético; ^{1}H RMN (400 MHz, $CDCl_3$): δ/ppm = 0,90 (m, 3H), 1,30 (m, 3H), 2,25 (d, 1H), 2,68 (d, 1H), 3,00 (m, 1H), 3,20 (m, 1H), 3,40 (m, 1H), 3,50 (m, 2H), 3,62 (s, 2H), 3,68 (s, 3H), 4,65 (m, 3H), 6,80 (m,

1H), 7,00 (t, 2H), 7,30 (m, 4H).

5-bromo-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético metiléster de ácido; ^{1}H RMN (400 MHz, $CDCl_3$). δ/ppm = 1,30 (m, 3H), 2,00 (m, 1H), 2,10 (m, 1H), 2,60 (d, 1H), 2,80 (m, 1H), 3,45 (m, 2H), 3,60 (m, 2H), 3,62 (s, 3H), 4,30 (m, 1H), 4,65 (m, 2H), 4,75 (d, 2H), 6,78 (d, 1H), 7,00 (t, 2H), 7,30 (m, 4H).

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico, ^{1}H RMN (400 MHz, DMSO-d_6): δ/ppm = 0,76-0,98 (m, 3H), 1,08-1,30 (m, 3H), 2,16 (m, 1H), 2,62 (m, 1H), 2,94 (m, 1H), 3,08 (m, 0,5H), 3,58 (m, 3H), 3,73 (s, 3H), 4,00 (m, 1H), 4,40 (s, 0,5H), 4,88 (m, 1,5H), 5,08 (m, 0,5H), 6,96 (m, 1H), 7,14 (m, 2H), 7,36 (m, 2H), 7,66 (m, 1H), 7,84 (m, 1H).

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico; ^{1}H RMN (400 MHz, DMSO-d_6): δ/ppm = 0,76-0,97 (m, 3H), 1,08-1,32 (m, 3H), 2,16 (m, 1H), 2,62 (m, 1H), 2,94 (m, 1H), 3,08 (m, 1H), 3,40 (m, 1,5H), 3,58 (m, 1H), 3,73 (s, 3H), 3,87 (s, 3H), 4,00 (m, 1H), 4,40 (s, 0,5H), 4,92 (m, 1,5H), 5,08 (m, 0,5H), 6,68 (m, 1H), 7,14 (m, 2H), 7,36 (m, 2H), 7,86 (s, 1H).

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico; ^{1}H RMN (500 MHz, DMSO-d_6). δ/ppm = 0,90 (m, 3H), 1,25 (m, 3H), 2,23 (m, 1H), 2,75 (m, 2H), 2,94 (m, 1H), 3,35 (m, 1H), 3,45 (m, 1H), 3,63 (m, 1H), 3,77 (s, 3H), 3,92 (s, 3H), 4,31 (s, 1H), 4,92 (m, 2H), 6,81 (s, 1H), 7,12 (m, 2H), 7,37 (m, 2H), 7,72 (s, 1H)

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metilbenzoico; ^{1}H RMN (400MHz, $CDCl_3$)· δ/ppm = 0,78-0,98(m, 3H), 1,18-1,36 (m, 3H), 2,22 (m, 1H), 2,38 (s, 3H), 2,66 (m, 1H), 3,00 (m, 1H), 3,10-4,20 (m, 4H), 3,86 (s, 3H), 4,24-4,86 (m, 3H), 6,94-7,02 (m, 3H), 7,29 (m, 2H), 7,81 (s, 1H)

metiléster de ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico; ^{1}H RMN (400 MHz, $CDCl_3$)· δ/ppm = 0,91 (d, 3H), 1,29 (d, 3H), 2,24 (d, 1H), 2,69 (dd, 1H), 3,02 (br, 1H), 3,41 (d, 1H), 3,47-3,71 (m, 2H), 3,87 (s, 3H), 4,10-4,22 (m, 1H), 4,60-4,86 (m, 3H), 7,00 (dd, 2H), 7,18 (br, 1H), 7,30 (dd, 2H), 7,91 (s, 1H)

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-

(trifluorometil)benzoico; ^{1}H RMN (400 MHz, $CDCl_3$) · δ/ppm = 1,00 (m, 3H), 1,30 (m, 3H), 2,25 (d, 1H), 2,70 (dd, 1H), 3,05 (m, 1H), 3,20 (m, 1H), 3,50 (m, 2H), 3,68 (m, 1H), 3,95 (s, 3H), 4,20 (m, 1H), 4,80 (m, 2H), 7,00 (t, 2H), 7,30 (m, 3H), 7,90 (s, 1H).

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]benzoico, ^{1}H RMN (400 MHz, DMSO-d_6): δ/ppm = 0,62 (m - rotámero, 1,25H), 0,73 (t - rotámero, 3,5H), 0,85 (m - rotámero, 1,25H), 1,23 (m, 1H), 1,37 (m, 1H), 1,55 (m, 1H), 1,70 (m, 1H), 1,83 (m, 1H), 2,26 (t, 1H), 2,55 (d, 1H), 2,75 (d - rotámero, 1H), 3,45 (dd, 1H), 3,47 (t, 1H), 3,60 (m, 1H), 3,78 (s, 3H), 4,20 (d, 1H), 4,90 (m - rotámero, 2H), 6,99 (d, 1H), 7,13 (t, 2H), 7,35 (t, 2H), 7,55 (dd, 1H), 7,64 (d, 1H).

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxibenzoico, . ^{1}H RMN (400 MHz, DMSO-d_6) δ/ppm = 0,60-0,90 (m, 6H), 1,06-1,60 (m, 3H), 1,62-1,82 (m, 1,5H), 2,16 (m, 1H), 2,60 (m, 2H), 2,88 (m, 1H), 3,46 (m, 1H), 3,60 (m, 1,5H), 3,76 (s, 3H), 3,85 (s, 3H), 4,22 (m, 1H), 4,92 (m, 1H), 5,12 (m, 1H), 6,68 (m, 1H), 7,12 (m, 2H), 7,34 (m, 2H), 7,86 (s, 1H).

metiléster de ácido 5-bromo-2-[2-[(2*R*)-4-[(5-cloro-2-tienil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético; ^{1}H RMN (400 MHz, $CDCl_3$) δ/ppm = 1,30 (m, 3H), 2,05 (m, 1H), 2,15 (m, 1H), 2,75 (m, 1H), 2,90 (m, 1H), 3,05 (m, 1H), 3,45 (m, 1H), 3,60 (m, 2H), 3,65 (s, 2H), 3,70 (s, 3H), 4,35 (m, 1H), 4,68 (m, 2H), 6,65 (d, 1H), 6,72 (d, 1H), 6,80 (dd, 1H), 7,35 (m, 2H).

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencensulfónico; ^{1}H RMN (400 MHz, DMSO-d_6) δ/ppm = 0,73-0,88 (m, 3H), 1,12-1,25 (m, 3H), 2,05-2,20 (m, 1H), 2,65 (m, 1H), 2,90 (m, 1H), 3,08 (m, 0,5H), 3,50 (m, 3H), 3,97 (m, 0,5H), 4,40 (m, 1H), 4,75 (m, 1,5H), 4,94 (m, 0,5H), 6,93 (m, 1H), 7,12 (m, 3H), 7,34 (m, 3H), 7,57 (m, 1H).

ácido 5-cloro-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencensulfónico; . ^{1}H RMN (400 MHz, DMSO-d_6 + TFA). δ/ppm = 1,16 (d, 3H), 1,32 (d, 3H), 2,76-3,50 (m, 5H), 4,24-4,52 (m, 3H), 4,60-5,00 (m, 3H), 6,50 (m, 1H), 7,23 (m, 2H), 7,30 (m, 1H), 7,54 (m, 2H), 7,67 (m, 1H), 9,50 (br, 1H).

EJEMPLO 3

Compuestos de Fórmula (Ia) y Fórmula (Ib)

A. A una solución de 1- ((3,4,5-trimetoxifenoxi)metil)car-

bonilpiperazina (0,22 g, 0,70 mmol) en ácido acético 1% en metanol (6 mL) se agregó 4-cianobenzaldehido (0,33 g, 2,5 mmol) y cianoborohidruro de sodio (0,093 g, 1,4 mmol) La mezcla resultante se agitó a temperatura ambiente durante 1,5 horas y la mezcla luego se concentró de volátiles al vacío. El residuo se capturó en acetato de etilo y se lavó con solución saturada acuosa de $NaHCO_3$, agua, y luego salmuera. La capa orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar un aceite amarillo La purificación por cromatografía de columna en gel de sílice dio 0,21 g de 1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-cianobencil)piperazina, un compuesto de fórmula (Ib), como un aceite límpido: RMN ($CDCl_3$) 7,6 (d, 2), 7,4 (d, 2), 6,2 (s, 2), 4,6 (s, 2), 3,8 (s, 6), 3,75 (s, 3), 3,6 (m, 4), 3,5 (s, 2), 2,2 (m, 4) ppm

B. en forma similar, se prepararon otros compuestos de fórmula (Ib):

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3,4-dimetoxibencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-metoxibencil) piperazina,

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3- clorobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-

trifluorometilbencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2,3-dimetil-4-metoxibencil) piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-fenoxibencil)piperazina,

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-(dimetilamino)bencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-(metiltio)bencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-metoxi3-metilbencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2-clorobencil)piperazina,

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-nitrobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-hidroxibencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3,5-dibromo-4- hidroxibencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2-fluorobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 2), 7,0 (m, 2), 6,2 (s, 2), 4,6 (s, 2) , 3,9 (m, 9), 3,6 (m, 4), 3,4 (s, 2), 2,4 (m, 4) ppm;

1-((3,4,5- trimetoxifenoxi)metil)carbonil-4-(4-bromobencil)piperazina; RMN ($CDCl_3$) 7,4 (d, 2), 7,2 (d, 2), 6,2 (s, 2), 4,6 (s, 2) , 3,85 (s, 6), 3,75 (s, 3), 3,6 (m, 4), 3,4 (s, 2), 2,4 (m, 4) ppm;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2-bromobencil) piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-fluorobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-bromobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-cianobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2,4-difluorobencil) piperazina,

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2,3-difluorobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3,4-difluorobencil)piperazina; RMN ($CDCl_3$) 7,3-7,0 (m, 3), 6,2 (s, 2), 4,6 (s, 2), 3,85 (s, 6), 3,75 (s, 3), 3,6 (m, 4), 3,5 (s, 2), 2,4 (m, 4) ppm;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2,6-difluorobencil)piperazina,

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-clorobencil)piperazina; RMN ($CDCl_3$) 7,2 (m, 4), 6,2 (s, 2), 4,6 (s, 2), 3,85 (s, 6), 3,75 (s, 3), 3,6

(m, 4), 3,5 (s, 2), 2,4 (m, 4) ppm;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-cloro-4-fluorobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-trifluorometilbencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-nitrobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(4-fluorobencil)piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(2,5-difluorobencil) piperazina;

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-nitro-4-hidroxibencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7. 2 (m, 4), 7,0 (t, 2), 6,8 (d, 2). 4,6 (s, 2), 3,6 (m, 4), 3,4 (s, 2), 2,4 (m, 4) ppm;

1-((4-clorofenoxi)metil)carbonil-4-(4-clorobencil)piperazina; RMN ($CDCl_3$) 7,2 (m, 6), 6,8 (d, 2), 4,6 (s, 2), 3,6 (m, 4), 3,5 (s, 2), 2,4 (m, 4) ppm,

1-((3,4,5-trimetoxifenoxi)metil)carbonil-4-(3-(benciloxi)bencil) piperazina;

1-((4-clorofenoxi)metil)carbonil-4-(3,4,5-trimetoxibencil)piperazina,

C. en forma similar, se prepararon los siguientes compuestos

de fórmula (Ia) se prepararon:

(3*S*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (s, 2), 4,0 (m, 2), 3,7 (m, 1), 3,4-2,9 (m, 3), 2. 7 (m, 1), 2,5 (m, 1), 2,1 (m, 1), 1,1 (m, 3) ppm;

(3*R*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (s, 2), 4,0 (m, 2), 3,7 (m, 1), 3,4-2,9 (m, 3), 3,2 (m, 1), 3,0 (m, 1), 2 7 (m, 1), 2,5 (m, 1), 2,1 (m, 1), 1,1 (m, 3) ppm;

1-((4-clorofenoxi)metil)carbonil-3-(2-((((4-clorofenoxi)metil)carbonil)oxi)etil)-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-hidroxietil-4-(4-fluorobencil)piperazina, sal diclorhidrato;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-metilpropil)amino)etil)-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,1 (m, 4), 6,9 (t, 2), 6,7 (d, 2), 4,6 (s, 2), 4,4 (d, 1), 3,6 (d, 1), 3,3 (m, 3), 2,7-2,3 (m, 6), 2,0-1,7 (m, 5) , 0,8 (t, 6) ppm;

1-((4-clorofenoxi)metil)carbonil-2-(2-((4-fluorobencil)amino)etil)-4-(4-fluorobencil)piperazina, sal clorhidrato;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-hidroxietil)

amino)etil)-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((metil)amino)etil)4-(4-fluorobencil)piperazina,

1-((4-clorofenoxi)metil)carbonil-3-(2-((4-fluorobencil)amino)etil)-4-(4-fluorobencil)piperazina, sal clorhidrato;

1-((4-clorofenoxi)metil)carbonil-3-(2-((metil)amino)etil)-4-(4- fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3-(2-((2-hidroxietil)amino)etil)-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3-(2-((2-metilpropil)amino)etil)-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((etil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (d, 2), 6,9 (t, 1), 6,4 (br s, 2), 5,0-4,6 (m, 3), 4,0 (m, 3), 3,7-3,2 (m, 4), 3,0-2 7 (m, 3) , 2,2 (m, 1), 1,3 (m, 6), 1,0 (br d, 3) ppm;

(*trans*)-1-((4-cloro-2-(((dietil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,5 (d, 1), 7,3 (m, 2), 7,2 (dd, 1), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 3), 4,2 (m, 1), 3,6-3,4 (m, 4), 3,2 (m, 1), 3,0 (m, 1), 2,7 (dd, 1), 2,6 (q, 2), 2,2 (d, 1), 1,3 (m, 3), 1,0 (m, 9) ppm;

(*trans*)-1-((4- cloro-2-(((ciclopropil)amino)metil)feno-

xi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (d, 2), 6,8 (t, 1), 4,8-4,0 (m, 6), 3,7-3,2 (m, 3), 3,0 (br s, 1), 2. 7 (d, 1), 2,2 (m, 2), 1,3 (m, 3), 0,9 (m, 3), 0,5 (m, 4) ppm;

(*trans*)-1-((4-cloro-2-(((dimetil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,1 (dd, 1), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 3), 4,1 (m, 1), 3,6-3,4 (m, 4), 3,0 (br s, 1), 2,7 (dd, 1), 2,2 (m, 8) , 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(((metil)amino)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,1 (dd, 1), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 2), 4,1 (m, 1), 3,7-3,4 (m, 5), 3,0 (br s, 1), 2,7 (dd, 1), 2,4 (s, 3) , 2,2 (m, 2), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4- cloro-2-((amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- luorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,1 (dd, 1), 7,0 (t, 2), 6,7 (d, 1), 4,7 (m, 2), 3,8 (d, 1), 3,5 (m, 4), 3,0 (br s, 1), 2,7 (dt, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((4-metilpiperazin-1-il)metil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-

fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,1 (dd, 1), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 4), 4,2 (m, 1), 3,8 (m, 1), 3,6-3,0 (m, 8), 2,9 (t, 1), 2,7 (m, 1), 2. 5-2,2 (m, 6), 1,3 (m; 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4- cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina; RMN (DMSO-d_6) 7,9 (m, 3), 7,7 (s, 2). 7,4 (t, 1), 7,2 (m, 2), 5,4 (d, 1), 5,0 (m, 2), 4,3 (m, 4), 3. 6- 3,1 (m, 12), 2,8 (m, 1), 1,5-1,0 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-(((2-hidroxietil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7. 3 (m, 4), 7,1 (dd, 1), 7,0 (t, 2), 6,7 (d, 1), 4,7 (m, 2), 4,2-3,4 (m, 6), 3,0 (br s, 2), 2,7 (m, 4), 2,2 (d, 2), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((morfolin-4-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 3), 7,1 (dd, 1), 7,0 (t, 2), 6,7 (d, 1), 4,7 (m, 2), 4,1-3,4 (m, 11), 3,0 (br s, 1), 2,7 (dd, 1), 2,5 (t, 4), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2- (etilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 3), 7,2 (dd, 1), 7,0 (t, 2), 6,8 (m, 1), 4,7 (m, 2), 4,1 (m, 1), 3,8 (s, 2), 3,6 (m, 1),

3,5 (q, 2) , 3,0 (m, 1), 2,7 (m, 3), 2,6 (q, 2), 1,3 (m, 3), 1,1 (t, 3), 1,0 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-((etil)(1-metilbutil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6) 7,9 (m, 1), 7,7 (m, 2), 7,5 (m, 1), 7,2 (m, 3), 5,1 (m, 1), 4,6 (d, 1), 4,3 (m, 2), 3,7-2,8 (m, 6), 2. 5 (s, 2), 1,5- 1,2 (m, 19), 0,8 (s, 3) ppm;

(*trans*)-1-((4-cloro-2-(bencilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 7), 7,0 (t, 2), 6,7 (d, 1), 6,6 (m, 2), 4,7 (d, 2), 4,4 (s, 2), 4,2-3,0 (m, 8), 2,6 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((1-metilbutil)amino) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 7,9 (m, 2), 7,3 (t, 2), 7,1 (m, 1), 6,9 (d, 2), 5,2 (d, 1), 4,9 (m; 2), 4,6 (m, 1), 4,5-3,2 (m, 6), 2,8 (t, 1), 2,5 (s, 1) , 1,7-1,2 (m, 9), 0,9 (d, 6) ppm;

(*trans*)-1-((4- cloro-2-((ciclopropilmetil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7. 3 (m, 3) 7,1 (dd, 1), 7,0 (t, 2), 6,8 (br d, 1), 4,7 (m, 2), 3,8 (s, 2), 3 6 (m, 1), 3,5 (q, 2), 3,0 (m, 2), 2,7 (dd, 1), 2,4 (m, 3), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 4),

0,4 (m, 2), 0,1 (m, 2) ppm,

(*trans*)-1-((4-cloro-2-(fenilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN (DMSO-d_6) 7,8 (m, 2) , 7,4 (m, 8), 7,2 (m, 2), 5,4 (d, 1), 5,0 (m, 2), 4,7 (m, 1), 4,5 (s, 2), 4 3 (m, 2), 3,9-3,4 (m, 4), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(1-((metil)(etil)amino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,4 (s, 1), 7,3 (m, 2), 7,1 (dd, 1), 7,0 (t, 2), 6,8 (br d, 1), 4,6 (br s, 3), 4,0 (m, 2), 3,6 (d, 1), 3,4 (d, 1), 3,0 (m, 1), 2,7 (dd, 1), 2,5 (d q, 1), 2,4 (d q, 1), 2,2 (s, 3), 1,3 (m, 6), 1,0 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-(1-(dimetilamino)etil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN (CD_3OD) 7,6 (m, 3), 7,5 (d, 1), 7,3 (m, 3), 5,1 (m, 3) , 4,4 (m, 2), 3,8 (dd, 2), 3,6 (m, 1), 3,4 (m, 1), 3,0 (m, 1), 2,6 (m, 7), 1,6 (m, 6), 1,3 (m, 3) ppm;

(2R)-1-((4-cloro-2-((4-*t*-butoxicarbonilpiperazin-1-il)metil)fenoxi)metil)carbonil-2-metil-4-(4- fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 3), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 2), 4,4 (m, 1), 3,5 (m, 10), 3,0 (m, 1), 2,8 (m, 1), 2,6 (m, 2), 1,4 (m, 12), 1,2 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((4-*t*-butoxicarbonilpiperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN (DMSO- d_6) 7,8 (m, 2), 7,6 (s, 1), 7,5 (m, 1), 7,3 (t, 2), 7,2 (m, 1), 5,4 (d, 1), 5,0 (m, 2), 4,7 (m, 1), 4,3 (m, 6), 4,0 (m, 2), 3,8-3,1 (m, 8) , 2,9 (m, 1), 1,4 (m, 12), 1,2 (m, 3) ppm;

1-((4-cloro-2-(morfolin-4-ilmetil)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11 5 (br d, 1), 10,6 (m, 1), 7,7 (m, 2), 7,6 (s, 1), 7,5 (dd, 1), 7,3 (t, 2), 7,2 (d, 1), 5,2 (q d, 2), 4,7 (m, 1), 4,4 (m, 4), 3,9-3,7 (m, 4), 3,5 (m, 1), 3,4 (m, 4), 3,0 (m, 4), 2,8 (m, 1), 1,5 (d, 1,5), 1,3 (d, 1,5) ppm.

ácido5-cloro-4-(dimetilamino)-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico; ^{1}H RMN (400 MHz, DMSO-d_6): δ/ppm = 1,10-1,30 (m, 6H), 2,82 (s, 6H), 3,00 (m, 1H), 3,21 (m, 0,5), 3,40 (m, 1H), 3,58-3,70 (m, 2H), 4,20-4,40 (m, 3H), 4,70 (m, 0,5H), 4,90-5,10 (m, 2H), 6,62 (s, 1H), 7,30 (t, 2H), 7,60 (m, 2H), 7,68 (m, 1H).

EJEMPLO 4

Compuestos de Fórmula (1a)

A. A una solución de (2*R*,5*R*)-1-((4- clorofenoxi)metil) car-

bonil-2-metil-4-(4-fluorobencil)-5-((hidroxi) metil)piperazina (0,17 g, 0,42 mmol) en CH_2Cl_2 (50 mL) a 0°C se agregó trietilamina (exceso) y cloruro de metansulfonilo (0,050 mL, 0,5 mmol). La mezcla resultante se agitó a 0°C hasta que se observó el consumo del alcohol mediante análisis TLC La mezcla de volátiles se concentró al vacío El residuo se capturó en DMF anhidra (5 mL) y se agregó K_2CO_3 (exceso), seguido por tetrazol (0,050 g, 0,71 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 días y se filtró. El filtrado se concentró al vacío y el residuo se capturó en acetato de etilo. Esto se lavó con agua, luego salmuera, luego se secó sobre $MgSO_4$ y se concentró al vacío para dar un aceite amarillo La purificación por cromatografía de columna en gel de sílice dio 25 mg de (2*R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((tetrazolil)metil) piperazina como un sólido blanco· RMN ($CDCl_3$) 7,3 (m, 5), 7,0 (m, 4), 4,8-4,1 (m, 5), 3,8 (m, 3), 3,2 (m, 2), 2,8 (dd, 1), 2,5 (dd, 1), 1,4 (d, 3) ppm, MS (ESI) 458

B. en forma similar, se prepararon los siguientes compuestos de fórmula (Ia):

(2*R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((1,2,4-triazol-2-il)metil)piperazina; RMN ($CDCl_3$) 7,9 (s, 1), 7,3(m, 5), 6,9 (m,

4), 4,7 (m, 3), 4,4-3,4 (m, 5), 3,1-2,7 (m, 2), 2,4 (t, 1), 2,0 (d, 1), 1,2 (m, 3) ppm;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((morfolin-4-il)metil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (d, 2), 4,7-4. 1 (m, 5), 3,9-3,4 (m, 9), 3,2-2,7 (m, 3), 2,3 (m, 2), 2,0 (m, 1), 1,2 (m, 3) ppm;

(2*R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((piperazin-1-il)metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((dietilamino)metil)pipera-zina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,7 (m, 3) , 3,9-3. 4 (m, 4), 2,8-2,3 (m, 7), 1,2 (m, 3), 0,9 (t, 6) ppm;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-(((etil)amino)metil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,7 (m, 3), 4,2-3,4 (m, 5), 2 8-2,3 (m, 6), 1,3-1,0 (m, 6) ppm,

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((4-metilpiperazin-1-il)metil)piperazina; RMN ($CDCl_3$) 7. 3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,7 (m, 3), 3,9-3,4 (m, 4), 2,8-2,2 (m, 14), 1,2 (m, 3) ppm,

1-((4-clorofenoxi)metil)carbonil-4-(4-fluorobencil)-3-

(2-(4-(*t*-butoxicarbonil)piperazin-1-il)etil) piperazina, sal clorhidrato

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5- ((dimetilamino)metil)piperazina

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-(((ciclopropil)amino)metil)piperazina

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((ciano)metil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (m, 4), 4,6 (m, 4), 4,2-3,2 (m, 4), 2,6-2,2 (m, 4), 1,2 (m, 3) ppm;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((((ciclopropil)metil)amino)metil)piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-(((2-hidroxietil)tio)metil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (d, 2), 4,7 (m, 3), 4,1-3. 5 (m, 5), 3,1-2,3 (m, 8), 1,3 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(imidazol-1-ilmetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($DMSO-d_6$) 11,3 (m, 1), 9 4 (s, 1), 7,9 (s, 3), 7,6 (s, 2), 7,4 (m, 1), 7,3 (m, 3), 7,1 (m, 1), 5,4 (m, 2), 4,9 (m, 1), 4,2 (m, 2), 3,8-3,2 (m, 6), 2,7 (m, 1), 1,4-1,2 (m, 6) ppm,

(*trans*)-1-((4-cloro-2-(1-(imidazol-1-il)etil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,6 (s, 1), 7,3 (m, 2), 7,2 (dd, 1), 7,0 (m, 5), 6,8 (d, 1), 5,8 (q, 1), 4,6 (m, 3), 4,2 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3,0 (m, 1), 2. 7 (dd, 1), 2,2 (dd, 1), 2,0 (br s, 1), 1,8 (dd, 3), 1,3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(triazol-1-ilmetilo)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 8,4 (s, 1), 7,9 (s, 1), 7,3 (m, 3), 7,0 (t, 2), 6,8 (d, 1), 5,4 (s, 2), 4,6 (m, 3), 4,2 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3,0 (m, 1), 2,9 (dd, 1), 2,2 (dd, 1), 1,3 (m, 3), 0,9 (m, 3) ppm, y

(*trans*)-1-((4-cloro-2-(tetrazol-1-ilmetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 9,4 (s, 1), 7,4 (s, 1), 7,3 (m, 3), 7,0 (t, 2), 6,8 (d, 1), 5,6 (s, 2), 4,7 (m, 3), 4,2 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3. 0 (m, 1), 2,9 (dd, 1), 2,2 (dd, 1), 1,3 (m, 3), 0,9 (m, 3) ppm.

EJEMPLO 5

Compuestos de Fórmula (Ia)

A. A una solución de cloruro de oxalilo (0,62 g, 5 mmol) en CH_2Cl_2 (20 mL) a -50°C se agregó DMSO (0,85 g, 11 mmol, en solución de 5 mL de CH_2Cl_2) a lo largo de 2 minutos.

Se agregó 4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxietil)piperazina (1,85 g, 4,5 mmol, en solución de 5 mL de CH_2Cl_2) La mezcla resultante se agitó a -50°C durante 15 minutos, luego se agregó trietilamina (2,3 g, 22 mmol) Después de 5 minutos a -50°C, la mezcla se entibió gradualmente hasta temperatura ambiente. En ese momento la mezcla se diluyó con CH_2Cl_2 y se lavó con agua, luego salmuera. La capa orgánica luego se secó sobre $MgSO_4$ y se concentró al vacío para dar 1,7 g de 4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-3-((formil)metil)piperazina como un aceite amarillo; RMN ($CDCl_3$) 9,8 (d, 1) 7,3 (m, 4), 7,0 (m, 4), 4,6 (m, 3), 3,8-3,2 (m, 7), 2,7-2,2 (m, 4) ppm.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (Ia)·

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-((acetil)metil)piperazina, sal clorhidrato, RMN ($CDCl_3$) 7,3 (m, 4), 6,9 (m, 4), 4,6 (m, 2), 3,8-3,3 (m, 7), 2. 4 (m, 4), 2,1 (d, 3) ppm; y

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5- formilpiperazina.

EJEMPLO 6

Compuestos de Fórmula (Ia)

A. A una solución de 4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-3-((formil)metil) piperazina (0,31 g,

0,77 mmol) en THF anhidro (20 mL) se agregó bromuro de metilmagnesio (0,26 mL, 0,77 mmol, 3,0 M solución en éter). La mezcla resultante se agitó durante la noche a temperatura ambiente. En ese momento la mezcla se virtió en NH_4Cl solución acuosa 5% y se extrajo con dos porciones de éter. Los extractos orgánicos combinados se lavaron con salmuera, luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar un aceite amarillo. La purificación por cromatografía flash en columna sobre gel de sílice dio 0,29 g de 4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxipropil)piperazina, como un aceite límpido e incoloro, que se convirtió en su sal clorhidrato, RMN ($CDCI_3$) 7,6 (m, 2), 7. 2 (m, 4), 6,9 (m, 2), 4,7 (m, 2), 4,4-3,0 (m, 10), 2,4-1,4 (m, 2). 1,3-1. 0 (m, 3) ppm.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (Ia)·

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxi-2-feniletil)piperazina; RMN ($CDCl_3$) 7,3 (m, 9), 7,0 (t, 2), 6,8 (d, 2), 4,9 (m, 1), 4,8 (m, 2), 4,1 (m, 1), 3,8-3,3 (m, 6), 2,8 (m, 2), 2,2 (m, 1), 2. 0 (m, 2) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxipentil)piperazina, RMN ($CDCl_3$) 7. 8 (m, 2), 7,3 (m, 4), 6,9 (d, 2), 4,8 (d, 2), 4,5-3,0 (m,

16) 2,2-1,2 (m, 8) , 0,9 (m, 3) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxibut-4-enil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (d, 2), 5,7 (m, 1), 5,2 (dd, 1), 5,1 (t, 1), 4,6 (m, 2), 4,2-3,3 (m, 7), 2,9 (m, 2), 2,4 (m, 1), 1,9-1,5 (m, 2) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxi-2-(4-metilfenil)etil)piperazina,

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-metil-5-(1-hidroxiprop-2-enil)piperazina, sal clorhidrato; RMN (DMSO-d_6) 10,1 (b s, 1), 7,6 (m, 2), 7,3 (d, 4), 6,9 (d, 2), 6,1 (m, 1), 5,9 (m, 1), 5,4 (m, 2), 4,8 (m, 2), 4,4 (m, 4), 3. 7-3,1 (m, 5), 1,1 (m, 3) ppm;

(2*R*, 5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-(1-hidroxibutil)piperazina, sal clorhidrato; RMN (DMSO-d_6) 10,3 (b s, 1), 7,6 (m, 2), 7,3 (m, 4), 6,9 (d, 2), 5,6 (m, 1), 4,9 (m, 2), 4,4 (m, 3), 3,9-3,1 (m, 5), 1,4 (m, 4), 1,1 (d, 3), 0. 8 (t, 3) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxibut-4-inil)piperazina;

4-(4-fluorobencil)-1- ((4-clorofenoxi)metil)carbonil-3-(2-hidroxi-2-ciclohexiletil) piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)car-

bonil-2-metil-5-(1-hidroxietil)piperazina sal clorhidrato, RMN (DMSO-d_6) 10,3 (b s, 1), 7,6 (m, 2), 7,3(m, 4), 6,9 (d, 2), 5,6 (b s, 1), 4,9 (m, 2), 4,6-4,0 (m, 6), 3,2 (m, 3), 1,2 (d, 3), 1,1 (d, 3) ppm;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1-hidroxi-1-(fenil)metil)piperazina, sal clorhidrato;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-5-(2-hidroxi-2- metilpropil)piperazina;

(*trans*)-1-((4-cloro-2-(1-hidroxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 3), 7,2-6,8 (m, 4), 5. 1 (m, 1), 4,7 (m, 2), 4,2-3,0 (m, 9), 2,7 (dd, 1), 2,3 (d, 1), 1,5 (d, 3), 1,3 (br m, 3), 0,9 (br m, 3) ppm;

1-((4-clorofenoxi)metil)carbonil-2-(1-hidroxietil)-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,2 (m, 4), 7,0 (m, 2), 6,8 (dd, 2), 4,7 (m, 3), 4,2 (m, 1), 3,8 (m, 1), 3,4 (s, 2), 3,2 (m, 1), 2,3 (dd, 1), 2,1 (m, 1), 1,1 (m, 3) ppm;

1-((4-clorofenoxi)metil)carbonil-2-(2- hidroxipropil)-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 7,6 (br s, 2), 7,3 (d, 4), 6,9 (q, 2), 4,9 (m, 3), 4,3 (m, 3), 3 9 (m, 3) , 3,3. (m, 2), 3,0 (m, 1), 2,2 (t, 1), 1,8 (m, 1), 1,5 (m, 1), 1 1 (d, 1,5) , 1,0 (d, 1,5)

ppm; y

1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxibut-3-enil)-4-(4-fluorobencil)piperazina; RMN (DMSO- d_6) 7,6 (dt, 2), 7,3 (m, 4), 6,9 (t, 2), 5,8 (m, 1), 5,2 (dd, 1), 5,0 (dt, 2), 4,8 (dt, 1), 4,4 (m, 2), 3,9 (m, 1), 3,4 (m, 3), 3,0 (m, 3), 2,2 (m, 1) , 1,8 (m, 1), 1,6 (m, 1) ppm

EJEMPLO 7

Compuestos de Fórmula (Ia)

A. A una solución de 4-(4- fluorobencil)-1-((4-clorofenoxi) metil)carbonil-3-(2-hidroxi-2-feniletil)piperazina (0,051 g, 0,11 mmol) en éter anhidro (5 mL) se agregó hidruro de sodio (0,006 g, 0,15 mmol). La mezcla resultante se agitó a temperatura ambiente durante 30 minutos, luego se agregó yoduro de metilo (0,016 g, 0,11 mmol). Luego de que el análisis por cromatografía en capa fina mostró que se había producido el consumo total de 4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxi-2-feniletil)piperazina, la mezcla se vertió en agua y se extrajo con dos porciones de éter. Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtró y se concentró al vacío para dar 0,046 g de 4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-metoxi-2- feniletil)piperazina como un aceite amarillo: RMN ($CDCl_3$) 7 3 (m, 9), 7,0 (m, 2), 6,9 (m, 2), 4,8 (m,

3), 4,2 (m, 2), 3,9-3,2 (m, 5), 3. 1 (d, 2), 3,0 (s, 1), 2,9 (s, 1), 2,6 (m, 1), 2,4 (m, 1), 1,9 (m, 1) ppm

B. en forma similar, se prepararon otros compuestos de la invención·

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((metoxi) metil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,6 (m, 3), 3,8-3,1 (m, 9), 3,0 (br s, 1), 2,7 (dd, 1), 2,3 (t, 1) , 1,2 (m, 3) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi) metil)carbonil-2-(2-(metoxi)etil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (d, 2), 4,7 (m, 3), 4,1 (m, 1), 3,7 (m, 1), 3,4-3,2 (m, 6), 2,8 (m, 3), 2,0 (m, 4) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(etoxicarbonil) metilpiperazin-2-ona,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonilpiperazin-2-ona;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-((metoxi)metil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,9 (dd, 2), 4,7 (d, 2), 3,9-3. 3 (m, 11), 2,6 (m, 2), 2,2 (m, 1) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2- (metoxi)etil)piperazina, RMN ($CDCl_3$) 7,3 (m, 4), 7. 0 (t, 2), 6,9 (dd, 2), 4,7 (d, 2), 3,8-3,3 (m, 11), 2,6 (m, 2), 2,2 (m, 1) , 1,8 (m, 2) ppm;

4-(4-fluorobencil)-1-(2-(4-clorofenoxi)etil) piperazin-2-ona, RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (d, 2), 4,2 (t, 2), 3,8 (t, 2), 3,5 (m, 4), 3,2 (s, 2), 2,6 (t, 2) ppm;

4-(4-fluorobencil)-1-(2-(4-clorofenoxi)etil)-3-((etoxicarbonil)metil)piperazin-2-ona, sal clorhidrato; RMN ($CDCl_3$) 7,2 (m, 2), 7,1 (m, 4), 6,8 (d, 2), 4,2 (m, 9), 3,5 (m, 5), 2,9 (br s, 1), 1,3 (t, 3) ppm;

(*trans*)-1-((4-cloro-2-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina, RMN ($CDCl_3$) 7,3 (m, 2), 7,0-6,8 (m, 5), 4. 7 (br m, 2,5), 4,2 (br s, 0,5), 3,8 (s, 3), 3,6-3,2 (m, 4), 3,0 (br s, 1), 2,7 (m, 1), 2. 2 (d, 1), 1,2 (br m, 3), 1,9 (br m, 3) ppm; y

(*trans*)-1-((5-cloro-2-metoxifenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 2), 7,0-6,8 (m, 5), 4,7 (br m, 2,5), 4,2 (br s, 0,5), 3,8 (s, 3), 3,6-3,2 (m, 4), 3,0 (br s, 1), 2,7 (m, 1), 2,2 (d, 1), 1,2 (br m, 3), 1,9 (br m, 3) ppm

EJEMPLO 8

Compuestos de fórmula (Ia)

A. A una solución de 4-clorobencilisocianato (0,59 g, 3,5 mmol) en THF anhidro (15 mL) a 0°C se agregó 1-(4-clorobencil) piperazina (0,74 g, 3,5 mmol). La mezcla

resultante se agitó a temperatura ambiente Después de 20 horas la mezcla se concentró de volátiles. El sólido resultante se lavó con acetato de etilo y se secó al vacío para dar 0,72 g de 1-(((4-clorobencil)amino) carbonil)-4-(4- clorobencil)piperazina como un sólido blanco; RMN ($CDCl_3$) 7,4 (m, 4), 7,3 (m, 2), 7,2 (m, 2), 4,4-4,1 (m, 6), 3,6 (m, 4), 3,0 (m, 2) ppm.

B. en forma similar, se prepararon otros compuestos de fórmula (Ia):

4-(4-fluorobencil)-1- ((4- clorofenoxi)metil)carbonil-2-(*N'*-metilureido)amino)metil) piperazina; RMN ($CDCl_3$) 7,2 (m, 4), 7,0 (t, 2), 6,8 (dd, 2), 5,7 (br s, 1), 5,2 (m, 1), 5,0 (m, 1), 4,8-2,0 (m, 15) ppm;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(*N'*-(etoxicarbonilmetil)ureido)metil)piperazina; RMN (DMSO-d_6) 7,3 (m, 4), 7,1 (t, 2), 6,8 (d, 2), 6,5 (t, 2), 4,8 (m, 2), 4,1-1,8 (m, 15), 1,1 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((aminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,8 (br s, 1), 8,3 (s, 1), 7,3 (m, 2), 7,0 (m, 3), 6,8 (d, 1), 6,0 (br s, 1), 5,0 (m, 2), 4,8 (m, 2), 4,1 (m, 3), 3,6 (m, 3), 3,1 (m, 2), 2,7 (d, 1), 2,3 (d, 1), 0,9 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-((aminocarbonil)(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluoro-

bencil)piperazina; RMN (DMSO-d_6) 9,8 (br m, 1), 9,4 (s, 1), 8,2 (s, 1), 7,6 (m, 2), 7,3 (m, 2), 7,0 (m, 2), 6,0 (br m, 2), 5,0 (m, 3), 4,3 (br m, 3), 4,0 (s, 2), 3,7-3,2 (m, 4), 2,8 (s, 3), 1,3 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-etiluredio)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 8,8 (s, 1), 8,4 (s, 1), 7,3 (m, 2), 7,0 (m, 2), 6,8 (m, 3), 4,7 (m, 2), 4,1 (m, 2), 3,6-3,3 (m, 4), 3. 0 (br s, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 5), 0,9 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diclorofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,4 (br d, 1), 9,2 (s, 1), 9,1 (s, 1), 8,2 (s, 1), 8,1 (d, 1), 7,7 (m, 2), 7,3 (m, 3), 6,9 (m, 2), 5,0 (m, 2), 4,7 (m, 1) , 4,3 (m, 3), 3,8 (q, 1), 3,6 (m, 1), 3,4 (m, 1), 2,9 (t, 1), 1,4 (m, 3), 1,2 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-(4-nitrofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,1 (s, 1), 8,4 (s, 1), 8,3 (s, 1), 8,2 (s, 1), 7,9 (d, 1), 7,8 (d, 1), 7,3 (m, 3), 7,0 (t, 2) , 6,8 (d, 1), 6,7 (m, 1), 4,7 (m, 2), 3,6 (m, 4), 3,1 (m, 1), 2,8 (m, 1), 2,3 (d, 1), 1,4 (m, 3), 1,0 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(*N'*-(4-metilfenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,5 (br d, 1), 9,6 (s, 1), 8,5 (d, 1), 8,2 (s, 1), 7,8 (m, 2), 7,3 (m, 4), 7 1 (d, 2), 6,9 (s, 1), 5,0 (m, 2), 4,3 (m, 3), 3,9 (s, 1), 3,6 (m, 1) , 3,4 (m, 1), 2,8 (dd, 1), 2,2 (s, 3), 1,4 (m, 3), 1,2 (m, 3) ppm,

(*trans*)-1-((4-cloro-2-(*N'*-bencilureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,0 (s, 1), 8,4 (s, 1), 7,3 (m, 8), 7,0 (t, 2), 6,8 (q, 2), 5,6 (t, 1), 4,6 (m, 4), 3,6 (m, 3), 3,0 (m, 1), 2,7 (m, 1), 2,2 (m, 2), 1 3 (m, 3), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(1-(*N*-metil-*N'*-etilureido)etil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (d, 1), 5,6 (m, 1), 5,4 (br d, 1) 4,7 (m, 2), 3,5 (q, 2), 3,2 (m, 4), 3,0 (m, 1), 2,7 (m, 4), 2,2 (d, 1), 1,4 (d, 3), 1,3 (m, 9), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(oxazol-2-ilaminometil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina, RMN ($CDCl_3$) 7,3 (m, 3), 7,2 (dd, 1), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 3), 4,4 (s, 2), 4,3 (t, 2), 3,9 (m, 1), 3,8 (t, 2), 3,5 (q, 2), 3,3 (m, 1), 3. 0 (m, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3),

0,9 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-(ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 7,3 (m, 4), 7,2 (m, 2), 7,1 (t, 2), 5,8 (br s, 1), 5,4 (br s, 2), 4,0 (m, 1), 3,4 (m, 2), 3,2 (m, 3), 2,9 (m, 1), 2,5 (m, 2), 2,1 (m, 1), 1,1 (m, 3), 0,8 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-2-(ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 7,3 (m, 5), 7,1 (t, 2), 6,6 (q, 1), 5,6 (br s, 2), 5,0 (m, 1), 4,4 (m, 0,5), 4,0 (m, 0,5), 3,5 (m, 2), 3,3 (m, 2), 2 8 (m, 2), 2,7 (m, 1), 2,5 (m, 1), 2,1 (d, 1), 1,2 (m, 3), 0,8 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((*N'*-(3-metoxifenil)ureido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6) 10,2 (br s, 1), 9,5 (s, 1), 8,5 (br s, 1), 8,2 (s, 1), 7,7 (m, 2), 7,2 (m, 4), 7,0 (s, 3), 6,5 (dd, 1), 5,0 (m, 2), 4,3 (m, 3), 3,7 (m, 5), 3,4 (m, 1), 2,9 (m, 1), 1,4 (s, 3), 1,2 (s, 3) ppm; y

(*trans*)-1-((4-cloro-2-((*N'*-(triclorometilcarbonil) ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10,5 (s, 1), 9,0 (m, 1), 8,3 (s, 1), 7,3 (m, 2), 7,0 (m, 4), 4,8 (m, 3), 4,2 (m, 1), 3,6 (m, 2) , 3,4 (m, 1), 3,0 (m,

1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm.

EJEMPLO 9

Compuestos de fórmula (Ia)

A A una solución de (*cis*)-1-((4- clorofenoxi)metil)carbonil-3,5-dimetilpiperazina (0,20 g, 0,71 mmol) en THF anhidro (2 mL) se agregó 4-fluorobencilbromuro de (0,11 mL, 0,85 mmol), diisopropiletilamina (0,15 mL, 0,85 mmol) y yoduro de sodio (0,042 g, 0,28 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2 días. En ese momento la mezcla se virtió en éter y se lavó con solución acuosa 5% de $NaHCO_3$, luego salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró al vacío para dar un aceite amarillo. La purificación por cromatografía de columna en gel de sílice dio 0,17 g de (*cis*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetil-4-(4- fluorobencil)piperazina como un aceite rosa; que se convirtió en su sal clorhidrato, RMN ($CDCl_3$) 7,6 (m, 2), 7,3 (m, 4), 7,0-6,8 (m, 2), 5,0-2,8 (m, 10), 1,5-1,3 (m, 6) ppm.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (Ia):

1-((4-clorofenoxi)metil)carbonil-2-((((ciclopropil)metil)amino)metil)-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,0

(t, 2), 6,8 (d, 2), 4,5 (s, 2) , 3,4 (m, 4), 3,0 (m, 1), 2,5 (m, 4), 2,2 (t, 1), 2,0 (m, 2), 16 (s, 2), 0,8 (m. 1), 0. 5 (m, 2), 0,1 (m, 2) ppm,

(3*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetilpiperazina, sal clorhidrato; RMN ($CDCl_3$) 13,3 (m,1), 7,9 (q, 2), 7,2 (m, 4), 6,9 (d, 2), 6,8 (d, 2), 4,8-3,3 (m, 10), 1,7 (d, 3), 1,2-1,0 (m, 3) ppm;

(3*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)me-til)carbonil-3,5-dimetilpiperazina, sal clorhidrato; RMN ($CDCl_3$) 13,3 (m,1), 7,9 (q, 2) , 7,2 (m, 4), 6,9 (d, 2), 6,8 (d, 2), 4,8-3,3 (m, 10), 1,7 (d, 3), 1,2-1. 0 (m, 3) ppm;

1-((4-clorofenoxi)metil)carbonil-2-(((4-fluorobencil)amino)metil)-4-(4-fluorobencil)piperazina,

1-((4-clorofenoxi)metil)carbonil-2-(((metil)amino)metil)-4-(4-fluorobencil) piperazina: RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (d, 2), 4,5 (q, 2), 3,6 (m, 4), 3,1 (m, 2), 2,8 (m, 3), 2,6 (s, 3), 2,5-2. 3 (m, 3) ppm; y

1-((4-clorofenoxi)metil)carbonil-3-trifluorometil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6,8 (dd, 2), 4,6 (m, 2), 4,2 (m, 1), 3,8 (m, 3), 3,6 (dd, 1), 3,3 (m, 2), 3,0 (m, 1), 2,6 (m, 1) ppm.

EJEMPLO 10

Compuestos de Fórmula (Ia)

A. A una solución de 1-((3,4,5-trimetoxifenoxi)metil)carbonil-2-(metoxicarbonil)metil-4-(4-fluorobencil)piperazina (0,20 g, 0,42 mmol) en una solución metanol/agua (20 mL, 3:1) se agregó hidróxido de litio, monohidratado(0,40 mL, 9,5 mmol). La mezcla resultante se agitó a temperatura ambiente durante 30 min. En ese momento el análisis HPLC mostró que se había producido la conversión completa. La mezcla se virtio en acetato de etilo y se lavó en forma consecutiva con una solución acuosa ácido acético/agua(pH < 4) , agua, y salmuera La capa orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar 0,060 g de 1-((3,4,5-trimetoxifenoxi)metil)carbonil-2-(carboxi)metil-4-(4-fluorobencil)piperazina como un sólido blanco; RMN ($CDCl_3$) 7,4 (m, 2), 7,1 (m, 2), 6,2 (m, 2), 5,1 (m, 1), 4,7 (m, 3), 4,0 (m, 2), 3. 8 (d, 9), 3,3-3,1 (m, 4), 2,6 (m, 2), 2,4 (m, 2) ppm, MS (ESI) 476

B. en forma similar, se prepararon los siguientes compuestos de la invención:

1-((4-clorofenoxi)metil)carbonil-3-(carboxi)metil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 7,4 (t, 2), 7,3 (d, 2), 7,1 (t, 2), 6,9 (d, 2), 4,7 (m, 2), 4,0 (d, 2), 3,7 (m, 2), 3,5 (m, 3), 3,2 (m, 1), 2,8-2,4

(m, 3) ppm;

1-((4-cloro-2-carboxifenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 8,0 (s, 1), 7,4 (dd, 1), 7,3 (m, 3), 7,0 (t, 1), 6,9 (d, 1), 5,0 (m, 2), 4,6 (m, 1), 4,3 (m, 1) , 3,7 (m, 1), 3,4 (m, 2), 2,8 (d, 1), 2,6 (m, 1), 2,1 (m, 1), 1,4 (d, 1,5), 1,3 (d, 1,5) ppm; y

(*trans*)-1-((4-cloro-2-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,4 (br s, 1), 8,0 (m, 1), 7,5 (m, 3), 7. 2 (m, 2), 7,0 (d, 1), 5,0 (m, 2), 4,6 (m, 1), 4,3 (m, 3), 3,7 (m, 2), 3,4 (m, 1) , 3,3 (m, 1), 1,4-1,3 (m, 6) ppm.

EJEMPLO 11

Compuestos de fórmula (Ia)

A. A una solución de hidruro de litio y aluminio (0,29 g, 7 mmol) en una solución de THF anhidro (16 mL) se agregó 1-((4-clorofenoxi)metil)carbonil-4-(4- fluorobencil)piperazina (0,36 g, 1,0 mmol, en 3 mL de THF). La mezcla resultante se agitó a temperatura ambiente durante 9 horas. En ese momento se agregaron 0,3 mL de agua y 0,3 mL de solución acuosa de NaOH al 15% y la mezcla resultante se agitó a temperatura ambiente. Después de 18 horas, la mezcla se filtró a través de una columna corta de Celite (THF) y el filtrado se concentró al vacío para dar 0,12 g de 1-(2-(4- clorofenoxi)etil)-4-(4-fluorobencil)piperazina co-

mo un aceite límpido, RMN ($CDCl_3$) 7,2 (m, 4), 7,0 (m, 2), 6,8 (m, 2), 4,0 (m, 2) , 3,4 (m, 2), 2,8-2,4 (m, 10) ppm.

B. en forma similar se prepararon los siguientes compuestos de fórmula (Ia) o (Ib):

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico, ^1H RMN (400 MHz, DMSO-d_6): δ/ppm = 0,84-0,98 (m, 3H), 1,16-1,28 (m, 3H), 2,16 (m, 1H), 2,70 (m, 1H), 2,88 (m, 1H), 3,08 (m, 0,5H), 3,40 (m, 1,5H), 3,58 (m, 1,5H), 4,0 (m, 1H), 4,40 (s, 0,5H), 4,94 (m, 1,5H), 5,18 (m, 0,5H), 7,12 (m, 3H), 7,36 (m, 2H), 7,54 (m, 1H), 7,62 (s, 1H)

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético; ^1H RMN (400 MHz, $CDCl_3$): δ/ppm = 1,00 (m, 3H), 1,30 (m, 3H), 2,05 (d, 1H), 2,68 (dd, 1H), 2,80 (m, 1H), 3,05 (m, 1H), 3,25 (m, 1H), 3,60 (m, 4H), 4,10 (m, 1H), 4,65 (m, 2H), 6,78 (m, 1H), 7,00 (t, 2H), 7,33 (m, 4H).

ácido 5-bromo-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético, ^1H RMN (400 MHz, $CDCl_3$). δ/ppm = 1,30 (m, 3H), 2,05 (m, 1H), 2,20 (m, 1H), 2,65 (d, 1H), 2,85 (m, 1H), 3,50 (m, 4H), 3,65 (m, 2H), 4,35 (m, 1H), 4,70 (m, 2H), 6,72 (d, 1H), 7,00 (t, 2H), 7,30 (m, 4H).

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-

dimetilpiperazinil]-2-oxoetoxi] benzoico; ^{1}H RMN (400 MHz, DMSO-d_6): δ/ppm = 0,80-0,98 (m, 3H), 1,16-1,28 (m, 3H), 2,16 (m, 1H), 2,55 (m, 0,5H), 2,70 (m, 0,5H), 2,95 (m, 1H), 3,08 (m, 0,5H), 3,40 (m, 1,5H), 3,58 (m, 1,5H), 4,00 (m, 1H), 4,40 (s, 0,5H), 4,94 (m, 1,5H), 5,18 (m, 0,5H), 7,12 (m, 3H), 7,36 (m, 2H), 7,64 (m, 1H), 7,74 (s, 1H).

ácidoz5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico;^{1}H RMN (400 MHz, $CDCl_3$)· δ/ppm = 0,84-0,98 (m, 3H), 1,16-1,28 (m, 3H), 2,16 (m, 1H), 2,70 (m, 1H), 3,08 (m, 2H), 3,50 (m, 2H), 3,72 (m, 1H), 3,92 (s, 3H), 4,20 (s, 0,5H), 4,94 (m, 2,5H), 6,54 (s, 1H), 7,00 (m, 2H), 7,34 (m, 2H), 8,24 (s, 1H).

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico;^{1}H RMN (500 MHz, DMSO-d_6): δ/ppm = 0,90 (m, 3H), 1,25 (m, 3H), 2,23 (m, 1H), 2,75 (m, 1H), 3,35 (m, 1H), 3,45 (m, 1H), 3,62 (m, 1H), 3,77 (m, 2H), 3,95 (s, 3H), 4,30 (s, 1H), 5,02 (m, 2H), 6,91 (s, 1H), 7,10 (m, 2H), 7,37 (m, 2H), 7,75 (s, 1H).

Ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metilbenzoico;^{1}H RMN (400MHz, DMSO-d_6 + D_2O): δ/ppm = 0,90-1,10 (m, 3H), 1,20-1,45 (m, 3H), 2,27 (m, 1H), 2,40 (s, 3H), 2,73

(m, 1H), 3,00-4,30 (m, 5H), 4,60-5,10 (m, 3H), 6,84 (s, 1H), 7,02 (m, 2H), 7,30 (m, 2H), 7,98 (s, 1H);

ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico; ^{1}H RMN (400 MHz, DMSO-d_6, 120°C): δ/ppm = 0,94 (d, 3H), 1,24 (d, 3H), 2,25 (d, 1H), 2,75 (dd, 1H), 2,95-3,00 (m, 1H), 3,34 (d, 1H), 3,47 (d, 1H), 3,61 (d, 1H), 3,73 (d, 1H), 4,24-4,30 (m, 1H), 4,94 (d, 1H), 5,03 (d, 1H), 7,09 (dd, 2H), 7,37 (dd, 2H), 7,41 (s, 1H), 7,81 (s, 1H).

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-(trifluorometil) benzoico; ^{1}H RMN (400 MHz, $CDCl_3$). δ/ppm = 1,00 (m, 3H), 1,30 (m, 3H), 2,30 (m, 1H), 2,70 (m, 1H), 3,10 (m, 1H), 3,25 (m, 1H), 3,60 (m, 2H), 3,70 (m, 1H), 4,65 (m, 1H), 5,00 (m, 2H), 7,00 (t, 2H), 7,30 (m, 3H), 8,05 (s, 1H).

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi] benzoico; ^{1}H RMN (500 MHz, DMSO-d_6, 120°C): δ/ppm = 0,62 (t - rotámero, 1,25H), 0,73 (t - rotámero, 3,5H), 0,86 (t - rotámero, 1,25H), 1,24 (m, 1H), 1,37 (m, 1H), 1,54 (m, 1H), 1,69 (m, 1H), 1,84 (m, 1H), 2,26 (t, 1H), 2,57 (d, 1H), 2,66 (dd, 1H), 2,90 (dd, 1H), 3,52 (m, 3H), 4,20 (d, 1H), 4,99 (m - rotamers, 2H), 7,09 (m, 3H), 7,35 (t,

2H), 7,55 (dd, 1H), 7,63 (d, 1H), 13,12 (br, 1H);

ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxibenzoico; ^{1}H RMN (500 MHz, DMSO-d_6): δ/ppm = 0,80 (m, 6H), 1,25 (m, 0,5H), 1,40 (m, 1H), 1,70 (m, 4H), 1,94 (m, 1H), 3,08 (m, 4H), 3,90 (m, 3,5H), 4,20 (br, 1H), 4,90 (m, 1H), 5,10 (m, 1H), 6,80 (m, 1H), 7,20 (m, 2H), 7,54 (m, 2H), 7,90 (s, 1H);

ácido 5-cloro-4-etoxi-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]- 2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 4-amino-5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxibenzoico;

ácido 4-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-5-metilbenzoico;

EJEMPLO 12

Compuestos de Fórmula (Ib)

A. A una solución de 1-(1-(*t*-butoxicarbonil)amino-2-(4-

clorofenil)etil) carbonil-4-(bencil)piperazina (0,20 g, 0,44 mmol) en una solución de CH_2Cl_2 (3 mL) se agregó ácido trifluoroacético (3 mL). La mezcla resultante se agitó a temperatura ambiente. Después de 18 horas, la mezcla se concentró al vacío para dar un aceite amarillo Éste se disolvió en acetato de etilo y se lavó con una solución acuosa de $NaHCO_3$. La capa orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar 0,17 g de una película transparente sin color. Ésta se disolvió en éter y se trató con una solución de HCl en éter, dando como resultado la formación de un precipitado blanco. La concentración dio 0,18 g de 1-(1-amino-2-(4-clorofenil)etil)carbonil-4-(bencil)piperazina como un sólido blanco, RMN ($CDCl_3$) 7,4 (m, 7), 7,1 (m, 2), 4,0 (t, 1), 3,7-3,1 (m, 4), 2,8 (m, 2), 2,4-2,2 (m, 5), 1,8 (m, 1) ppm.

B. en forma similar, se prepararon los siguientes compuestos de fórmula (Ib):

1-(3-amino-2-(4-clorofenil)propil) carbonil-4-(4-clorobencil)piperazina; RMN ($CDCl_3$) 7. 2 (m, 8), 3,8 (s, 3), 3,6-3,3 (m, 8), 3,0 (m, 2), 2,6 (dq, 2), 2,4-2,1 (m, 4) ppm; y

1-(1-amino-2-(4-clorofenil)etil)carbonil-4-(4- clorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 6), 7,1 (d, 2), 4,0 (t, 1), 3,6-3,1 (m, 6), 2,8 (dq, 2), 2,6 (br s,

2), 2,4 (m, 3) , 1,8 (m, 1) ppm.

C. en forma similar, se prepararon los siguientes compuestos de fórmula (Ia):

(*trans*)-1-((4-cloro-2-(aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7. 3 (m, 3), 7,2 (dd, 1), 7,0 (t, 2), 6,8 (br d, 1), 4,7 (m, 2), 3,9 (s, 2), 3. 5 (m, 3), 3,0 (br s, 1), 2,7 (m, 1), 2,2 (m, 4), 1,3 (m, 3), 0,9 (m, 3) ppm;

(trans)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 10,1 (s, 1), 8,5 (s, 1), 7,3 (t, 3), 7,0 (t, 3), 6,8 (d, 1), 4,7 (m, 3), 4,2-3. 4 (m, 5), 3,2 (m, 1), 3,0 (br s, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,3 (m, 3), 0,9 (m, 3) ppm;

(2*R*,5*S*)-1-((4-cloro-2-(glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 10,0 (s, 1), 8,2 (m, 3), 7,6 (s, 1), 7,3 (m, 2), 7,1 (dd, 1), 6,9 (m, 1), 5,2-4,2 (m, 5), 3,8-2,9 (m, 7), 1,2 (m, 6) ppm;

(2*R*)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 11. 4 (br s, 1), 10,0 (s, 1), 8,3 (br s, 2), 8,1 (s, 1), 7,8 (m, 2), 7,4 (t, 2), 7,1 (d, 1), 7,0 (d, 1) 5,0 (q, 2), 4,7 (m, 1), 4,3 (m, 3), 3,9 (m, 3), 3,6

(m, 1), 3,1 (m, 3), 1,5 (d, 1,5), 1,3 (d, 1,5) ppm;

(*trans*)-1-((4-cloro-2-((*N'*-metilglicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,9 (s, 1), 8,5 (s, 1), 7,3 (m, 3), 7,0 (m, 3), 6,8 (d, 1), 4,7 (m, 3), 4,2-3,9 (m, 1), 3,6-3,3 (m, 5), 3,0 (br s, 1), 2,7 (dd, 1), 2. 5 (s, 3), 2,3 (d, 1), 1,3 (m, 3), 1,0 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-(alaninamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, RMN ($CDCl_3$) 10. 2 (s, 1), 8,5 (s, 1), 7,3 (m, 3), 7,0 (m, 3), 6,8 (d, 1), 4,7 (m, 3), 4,2- 3,9 (m, 1), 3,6-3,2 (m, 5), 3,0 (m, 1), 2,7 (dd, 1), 2,2 (d, 1), 1,4 (d, 3), 1,3 (m, 3), 1,0 (br s, 3) ppm;

(*trans*)-1-((4-cloro-2- (1-(metilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 3), 7,1 (dd, 1), 7,0 (t, 2), 6,8 (br d, 1), 4,7 (m, 3), 4,0 (q, 2), 3,6 (q, 2), 3. 2 (m, 1), 3,0 (m, 1), 2,7 (dd, 1), 2,3 (m, 4), 1,3 (m, 6), 0,9 (m, 3) ppm;

(*trans*)-1-((4-cloro-2-((metilamino)(fenil)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN ($CDCl_3$) 7,6 (br d, 1), 74-7,1 (m, 8), 7,0 (t, 2), 6,8 (m, 1), 5,0 (d, 1), 4,6 (m, 3), 4,2 (m, 1), 3,5 (t, 1), 3,4-3,0 (m, 4), 2. 8 (m, 1), 24 (s, 3), 2,2 (m, 1), 1,2 (m, 3), 0,8 (m, 3) ppm;

(2*R*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 9,2 (br s, 1), 7,6 (m, 4), 7,3 (t, 2), 7,2 (d, 1), 5,2 (dd, 1), 5 0 (d, 1), 4,8 (m, 1), 4,4 (d, 4), 3,9 (d, 1), 3,4 (m, 11), 1,4 (d, 1,5), 1. 2 (d, 1,5) ppm;

(2*R*,5*S*)-1-((4-cloro-2- ((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 9,8 (br s, 1), 9,2 (br s, 1), 7,6 (s, 3), 7,5 (dd, 1), 7,3 (t, 2), 7,2 (d, 1), 5,4 (m, 1) , 5,0 (m, 3), 4,7 (m, 1), 4,5 (s, 2), 4,3 (m, 3), 3,7-3,1 (m, 11), 1,4-1. 1 (m, 6) ppm;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO- d_6) 11,3 (br d, 1), 9,7 (m, 2), 7,9 (m, 2), 7,7 (m, 2), 7. 4-7,2 (m, 3), 5,4 (m, 1), 5,0 (m, 2), 4,6 (m, 1), 4,2 (m, 3), 3,8-3,2 (m, 10), 2,8 (dd, 1), 1,7 (m, 3), 1,4 (dd, 3), 1,2 (m, 3) ppm;

(*trans*)-1-(2-(4-clorofenil)-3-(amino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;RMN ($CDCl_3$) 7,3 (m, 4), 7. 2 (d, 2), 7,0 (t, 2), 4,8 (m, 1), 4,2 (m, 1), 3,9 (m, 1), 3,5-3,2 (m, 3), 2. 9 (m, 3), 2,6 (m, 2), 2,2 (m, 1), 1,2 (m, 3), 0,8 (m, 3) ppm; y

(*trans*)-1-(2-(4-clorofenil)-2-(amino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7.

3 (m, 6), 7,0 (t, 2), 4,7 (m, 0,5), 4,5 (m, 1), 4,2 (d, 0,5), 3,5 (q, 2), 3. 2 (m, 1), 3,0 (m, 1), 2,6 (m, 2), 2,5 (m, 2), 2,2 (m, 1), 1,2 (m, 3), 0. 9 (m, 3) ppm.

EJEMPLO 13

Compuestos de Fórmula (Ia)

A. A una solución de (*trans*)- 1-((4-cloro-2-carboxifenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina (0,217 g, 0,50 mmol) en una solución de tetrahidroduran (5 mL) a 0°C se agregó cloroformato de isobutilo (0,075 g, 0,55 mmol) y *N*-metilmorfolina (0,0556 g, 0,55 mmol). La mezcla resultante se agitó a 0°C durante 20 min, dando como resultado la formación de un precipitado blanco Luego se agregó una solución de metilamina en tetrahidrofurano (0 25 mL, 2,0 M, 0,50 mmol) y la mezcla se agitó durante 30 min más, momento en el cual se concentró de volátiles al vacío. El sólido resultante se disolvió en acetato de etilo y se lavó con agua, luego salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a 0,208 g de una espuma. Ésta se disolvió en acetato de etilo y se trató con solución 1 M de HCl en éter (exceso). El sólido resultante se recogió por filtration y se lavó con acetato de etilo. El secado al vacío dio 0,19 g de (*trans*)-1-((4-cloro-2- (metilaminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluoroben-

cil)piperazina como un sólido blanco; RMN (DMSO-d_6) 10,8 (br d, 1), 9,2 (br s, 1), 7,8 (s, 2), 7,7 (m, 1), 7,6 (m, 1), 7,3 (m, 3), 5,4 (d, 1), 5,0 (m, 2), 4,7 (m, 1), 4,3 (m, 3), 4,0 (m, 1), 3,6 (m, 2), 2. 8 (s, 3), 1,4 (m, 3), 1,3 (m, 3) ppm

B. en forma similar, se prepararon los siguientes compuestos de fórmula (la):

(*trans*)-1-((4-cloro-2-((aminocarbonilmetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN (DMSO-d_6) 9,4 (br s, 1), 7,8 (s, 1), 7,6 (dd, 1), 7,4 (m, 2), 7,2 (d, 1), 7,1 (t, 2), 7,0 (s, 1), 5,3 (m, 1), 5,0 (m, 2), 4,4 (m, 1), 4,0 (m, 1), 3,8 (d, 2), 3,5 (m, 2) , 3,0 (m, 1), 2,7 (m, 1), 2,2 (br d, 1), 1,2 (br d, 3), 0,9 (br d, 3) ppm,

(*trans*)-1-((4-cloro-2-((2-aminoetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 9,4 (br s, 1), 8,2 (s, 1), 7,3 (m, 3), 7,0 (t, 2), 6,8 (d, 1), 4,7 (m, 3), 4,2 (m, 1) 3,6 (m, 5), 3,1 (m, 3), 2,7 (br d, 1), 2,3 (d, 1), 1,3 (br d, 3), 1,0 (m, 2) ppm;

(*trans*)-1- ((4-cloro-2-((4-aminocarbonilfenil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina; RMN (DMSO-d_6) 11,4 (s, 1), 7,9 (m, 5), 7,7 (d, 1), 7,4 (m, 3), 7,1 (t, 2), 5,4 (d,

1), 5,1 (m, 2), 4,6 (br s, 1), 4,0 (m, 1), 3,5 (m, 3), 3. 0 (m, 1) , 2,2 (m, 1), 1,3 (m, 3), 0,9 (m, 3) ppm; y

(*trans*)-1-(2-(4-clorofenil)-3-(*t*-butoxicarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; RMN ($CDCl_3$) 7,3 (m, 4), 7,2 (d, 2), 7,0 (t, 2), 4,8 (br s, 1), 4,6 (m, 1), 4,0 (m, 1), 3,4 (m, 6), 3,0 (m, 1), 2,6 (m, 2), 2,1 (m, 1), 1,4 (s, 9) , 1,2 (m, 3), 0,9 (m, 3) ppm.

EJEMPLO 14

Compuestos de fórmula (Ia)

A. A una solución de clorhidrato de hidroxilamina, (0,17 g, 2,5 mmol) en DMSO (3 mL) se agregó trietilamina (0,252 g, 2,5 mmol). La mezcla se agitó a temperatura ambiente durante 10 minutos, luego se filtró y se lavó con THF. El filtrado se concentró al vacío para eliminar el THF luego se trató con (*trans*)-1-((4-cloro-2-cianofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina (0,200 g, 0,48 mmol) La mezcla resultante se calentó a 75°C durante 20 horas. En ese momento la mezcla se diluyó con agua y se extrajo con acetato de etilo. El extracto orgánico se lavó con agua, luego salmuera, se secó sobre $MgSO_4$, se filtró se concentró al vacío para dar 0,21 g de un aceite. 0,030 g de este aceite se disolvió en acetato de etilo y se trató con solución 1 M de HCl

en éter (exceso). El sólido resultante se recogió por filtración y se lavó con acetato de etilo. El secado al vacío dio 0,027 g de (*trans*)-1-((4-cloro-2-(hidroxiamidino)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina como un sólido blanco; RMN ($CDCl_3$) 7,6 (s, 1), 7,3 (t, 2), 7,2 (dd, 1) , 7,0 (t, 2), 6,7 (br d, 1), 6,1 (br s, 2), 4,7 (m, 3), 3,7 (br d, 1), 3. 5 (q, 2), 3,2 (m, 1), 3,0 (m, 1), 2,7 (m, 1), 2,2 (t, 1), 1,3 (m, 3), 0,9 (m, 3) ppm.

EJEMPLO 15

Compuestos de Fórmula (Ia)

A. A una solución de 4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxietil)piperazina (0,134 g, 0,33 mmol) y trifenilfosfina (0,100 g) en THF (6 mL) a 0°C se agregó azodicarboxilato de dietilo (0,060 mL) y difenilfosforilazida (0,081 mL). La mezcla se agitó a temperatura ambiente durante 2 días, luego se concentró de volátiles al vacío. La purificación por cromatografía de columna en gel de sílice dio 0,047 g de 1-((4-clorofenoxi)metil)carbonil-2-(2-azidoetil)-4-(4-fluorobencil)piperazina como un aceite límpido e incoloro; RMN ($CDCl_3$) 7,3 (m, 4), 7,0 (t, 2), 6. 9 (d, 2), 4,7 (m, 3), 4,4 (br d, 1), 4,3 (m, 1), 4,1 (m, 1), 3,5-3,1 (m, 4), 2,8 (d, 1), 2,7 (d, 1), 2,1 (m, 2), 1,8 (m, 1) ppm.

EJEMPLO 16

Compuestos de Fórmula (Ia)

A. A una solución de (*trans*)-1-((4-cloro-2-aminofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina (0,169 g, 0,416 mol) en 10 mL de cloruro de metileno se agregó anhidrido ftálico (0,074 g, 0,499 mol) y varios tamices moleculares de 4Å. La mezcla se agitó a temperatura ambiente durante 3 horas, luego a 70°C durante 3 horas. En ese momento la mezcla se enfrió a 0°C y se trató con cloruro de oxalilo (0,064 g, 0,499 mol). Esto se agitó a temperatura ambiente durante 3 horas luego se particionó entre cloruro de metileno y agua. La capa orgánica se concentró para dar un aceite. La purificación por cromatografía de columna en gel de sílice dio 0,058 g de un aceite claro. Éste se disolvió en acetato de etilo y se trató con solución 1M de HCl en éter (exceso). El sólido resultante se recogió por filtración y se lavó con acetato de etilo El secado al vacío dio 0,045 g de (*trans*)-1-((4-cloro-2-(ftalimido)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina como un sólido blanco; RMN ($CDCl_3$) 7,9 (m, 2), 7,8 (m, 2), 7,4 (d, 1), 7,3 (m, 3) , 7,05 (d, 1), 7,0 (t, 2), 4,6 (m, 3), 4,0 (m, 1), 3,5 (m, 1), 3,4 (m, 2), 2,9 (m, 1), 2,6 (m, 1), 2,2 (m, 1), 1,2 (m, 3), 0,9 (m, 3) pppm.

B. en forma similar, se preparó el siguiente compuesto de fórmula (Ia):

(*trans*)-1-((4-cloro-2-(maleimido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;RMN ($CDCl_3$) 7,3 (m, 6), 7,0 (t, 2), 6,8 (s, 1), 4,6 (m, 3) , 4,0 (m, 1), 3,5 (q, 2), 3,2 (m, 1), 3,0 (br s, 1), 2,6 (dd, 1), 2,2 (br d, 1), 1,2 (m, 3), 0,9 (m, 3) ppm.

EJEMPLO 17

Este ejemplo ilustra la preparación de composiciones farmacéuticas representativas para administración oral que contienen un compuesto de la invención, o una sal aceptable para uso farmacéutico de los mismos, por ejemplo, 1-((2- metilfenoxi)metil)carbonil-4-(4-clorobencil) piperazina sal clorhidrato·

A. Ingredientes	% p/p
Compuesto de la invención	20,0%
Lactosa	79,5%
Estearato de magnesio	0,5%

Los ingredientes precedentes son mezclados y dispensados en cápsulas de gelatina de cubierta dura que contienen 100 mg cada una, una cápsula contiene aproximadamente una dosis diaria total

B. Ingredientes	% p/p
Compuesto de la invención	20,0%
Estearato de magnesio	0,9%
Almidón	8,6%
Lactosa	69,6%

PVP (polivinilpirrolidina) 0,9%

Los ingredientes precedentes con la excepción del estearato de magnesio son combinados y granulados utilizando agua como líquido de granulación. La formulación es luego secada, mezclada con el estearato de magnesio y formada en tabletas con una máquina tableteadora apropiada

C. Ingredientes

Compuesto de la invención	0,1 g
Propilenglicol	20,0 g
Polietilenglicol 400	20,0 g
Polisorbato 80	1,0 g
Agua	q s 100 mL

El compuesto de la invención se disuelve en Propilenglicol, Polietilenglicol 400 y Polisorbato 80. Luego se agrega una cantidad suficiente de agua con agitación para dar 100 mL de la solución que es filtrada y envasada.

D. Ingredientes	% p/p
Compuesto de la invención	20,0%
Aceite de maní	78. 0%
Span 60	2,0%

Los ingredientes precedentes son fundidos, mezclados y vertidos en cápsulas elásticas blandas.

E. Ingredientes	% p/p
Compuesto de la invención	1,0%
Metil o carboximetilcelulosa	2,0%

solución salina 0,9% q.s 100 mL

El compuesto de la invención se disolvió en la solución salina / celulosa, se filtró y se envasó para el uso.

EJEMPLO 18

Este ejemplo ilustra la preparación de una composición farmacéutica representativa para administración parenteral que contiene un compuesto de la invención, o una sal aceptable para uso farmacéutico del mismo, por ejemplo, 4- (4-fluorobencil)-1-((2-((acetilamino)metil)-4-clorofenoxi)metil) carbonil-2,5-metilpiperazina:

Ingredientes	
Compuesto de la invención	0,02 g
Propilenglicol	20,0 g
Polietilenglicol 400	20,0 g
Polisorbato 80	1,0 g
solución salina 0,9%	q s 100 mL

El compuesto de la invención se disuelve en Propilenglicol, Polietilenglicol 400 y Polisorbato 80. Luego se agrega una cantidad suficiente desolcuión salina 0,9% con agitación para dar 100 mL de la solución I.V. que es filtrada a través de un filtro de membrana de 0,2 m y envasado en condiciones estériles.

EJEMPLO 19

Este ejemplo ilustra la preparación de a representative pharmaceutical composition en suppository form que con-

tienen un compuesto de la invención, o una sal aceptable para uso farmacéutico de los mismos, por ejemplo, 4- (4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxietil) piperazina:

Ingredientes	% p/p
Compuesto de la invención	1,0%
Polietilenglicol 1000	74,5%
Polietilenglicol 4000	24,5%

Los ingredientes son melted juntos y mixed on a steam bath, y poured into molds containing 2,5 g total weight

EJEMPLO 20

Este ejemplo ilustra la preparación de una composición farmacéutica representativa para insuflación que contiene un compuesto de la invención, o una sal aceptable para uso farmacéutico del mismo, por ejemplo, (2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2,5-dimetilpiperazina:

Ingredientes	% p/p
Compuesto de la invención micronizado	1,0%
Lactosa micronizada	99,0%

Los ingredientes se muelen, mezclan y envasan en un insuflador equipado con una bomba dosificadora

EJEMPLO 21

Este ejemplo ilustra la preparación de una composición farmacéutica representativa en forma nebulizada que contie-

nen un compuesto de la invención, o una sal aceptable para uso farmacéutico de los mismos, por ejemplo, 1-(((4- cloro-fenil)amino)metil)carbonil-4-(4-clorobencil)piperazina:

Ingredientes	% p/p
Compuesto de la invención	0,005%
Agua	89,995%
Etanol	10,000%

El compuesto de la invención se disuelve en etanol y se mezcla con agua. La formulación luego se envaza en un neulizador equipado con una bomba dosificadora.

EJEMPLO 22

Este ejemplo ilustra la preparación de una composición farmacéutica representativa en forma de aerosol que contiene un compuesto de la invención, o una sal aceptable para uso farmacéutico del mismo, p.ej., 1-((4-cloro-2-(((etil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina:

Ingredientes	% p/p
Compuesto de la invención	0,10%
Propelente 11/12	98,90%
Ácido oleico	1 00%

El compuesto de la invención se dispersa en ácido oleico y lso propelentes La mezcla resultante luego se vierte en un recipiente para aerosol equipado con una válvula dosificadora

En los siguientes ejemplos se utilizan células 293MR. Las mismas son células embriónicas de riñón humano (HEK293) que se transfectaron de manera estable para expresar el receptor CCR1 humano mediante el siguiente procedimiento: se obtuvieron células HEK293 de la American Type Culture Recolección (ATCC CRL 1573). El cADN humano de CCR1 se consiguió gracias a la colaboración con el Dr. Stefen Peiper de la University of Louisville, Kentucky. El gen del CCR1 se subclonó utilizando técnicas estándar (véase, por ejemplo, *Molecular Cloning· A Laboratoriy Manual, 2a Edición, frío Spring* Harbor Laboratory Press, 1989) en un plásmido estándar que contiene el promotor e intensificador del SV40. El plásmido también contenía genes de resistencia a la higromicina y puromicina. Se utilizaron protocolos de transfección estándar con fosfato de calcio para insertar el plásmido en las células HEK293. Las células se seleccionaron según su expresión estable del CCR1 utilizando selección con higromicina y puromicina Se probó la capacidad de las células de unir con alta afinidad RANTES o MIP-1α marcados con ^{125}I.

EJEMPLO 23

Ensayo *In Vitro*· Flujo de calcio

Como el receptor CCR1, en común con otros siete receptores transmembrana acoplados con proteína G, responde a la unión de su ligando, *por ejemplo*, MIP-1α y RANTES, movilizando el calcio intracelular libre, se puede medir la acti-

vidad biológica mediante ensayos de flujo de calcio utilizando la tintura fluorescente Fura 2. En el siguiente ensayo, se midió la capacidad de los compuestos de la invención de bloquear dicha respuesta biológica

Protocolo:

1) las células 293MR de dos matraces se desprendieron, se lavaron y se resuspendieron en Hanks Ca^{2+} (50ml de Hanks, 1,0ml de Hepes 1M, 1,6ml de $CaCl_2$ 500mM, pH 7,4) Las células se lavaron dos veces en dichos medios.

2) Se contaron las células CCR1= 28 x 10^6 células se llevaron a 2 x 10^6 células/ml suspendiéndolas en 14ml de Hanks Ca^{2+}.

3) a 10ml de las células (20 x 10^6) se les agregó 30ml de medio (con 50µg de Fura en 50µl de DMSO). La concentración final de células fue de 1,0 x 10^6 células/ml. La concentración final de Fura fue 1,25µM.

4) las células se incubaron a 37°C durante 30 minutos en presencia (o ausencia) de concentraciones crecientes de los compuestos de la invención Las células se lavaron según se acaba de decir para eliminar la Fura libre. Las células se resuspendieron a 1 x 10^6 células/ml. Luego se tomó una alícuota de las células (2,0 ml) en una cubeta y se puso en un espectrofluorímetro Luego se estimularon las células tanto con MIP-1α como con RANTES (Peprotech Inc) y se midió la liberación de Ca^{2+} en el espectrofluorímetro.

5) Los datos se corrigieron para nM de Ca^{2+} liberado agregando 100µl de 0,1% de Triton X-100 (para los valores máximos) seguido de 100µl de EGTA 500mM, pH 8,5 (para los valores mínimos).

Al probar los compuestos de la invención en este ensayo, demostraron la capacidad de inhibir la movilización de Ca^{2+} en respuesta a la unión de MIP-1α y RANTES con el receptor CCR1

EJEMPLO 26

Ensayo *In Vitro:*

Los ensayos se llevaron a cabo en un microfisiómetro para investigar la actividad funcional del antagonista de interés. El microfisiómetro evalúa la respuesta celular mediante el uso de un sensor potenciométrico a base de silicio que puede medir pequeños cambios en el pH de la solución (Hafeman *et al., Science* (1988), Vol. 240, pp. 1182-1185; Parce *et al., Science* (1989), Vol. 246, pp. 243-247). Se ha mostrado que el microfisiómetro se puede utilizar para medir tasas metabólicas de células vivas (Parce *et al.*, 1989). La activación de los receptores de la membrana celular puede alterar la velocidad de la acidificación extracelular (Owicki *et al., Proc. Natl. Acad Sci* (1989), Vol. 87, pp 4007-4011). El siguiente ensayo demuestra que la activación del receptor CCR1 se expresa de manera endógena en células THP-1 humanas obteniéndose cambios fisiológicos inducidos por MIP-

1α y RANTES que causan un aumento de las tasas metabólicas y que los compuestos de la invención inhiben dicho efecto de manera dependiente de la dosis.

Materiales

1. Conjunto de elementos de cápsula citosensora (Molecular Devices Cat #R8013).

2. Medio de inclusión en agarosa (Molecular Devices Cat. #R8023).

3. Medio modificado para citosensor RPMI 1640, con amortiguación suave del pH (Molecular Devices Cat. #R8023).

4. conjunto de elementos Sterilant para el citosensor (Molecular Devices Cat. #R8017)

5. Conjunto de elementos de mantenimiento para el electrodo de referencia (Molecular Devices Cat. # 0310-2805).

6. Solución de trabajo de MIP-1α o RANTES (Peprotech Inc.). 10μM en medio RPMI 1640 modificado (Molecular Devices Cat. #R8016) suplementado con 1mg/ml de BSA (seroalbúmina bovina), 100 unidades/ml de penicilina, y 100μg/ml de estreptomicina). Dicha solución de trabajo se denominará de aquí en adelante "medio de cultivo modificado".

7 Solución de trabajo de MCP-1: 10μM en medio de cultivo modificado.

8. Solución madre de compuestos de la invención: 1mM en DMSO (almacenada a temperatura ambiente).

9. cultivo de células·

a. THP-1 (ATCC Cat. # TIB202).

b. Medio de cultivo de tejido: RPMI 1640 suplementado con 10% de FBS (suero fetal bovino) Dicho medio se denominará de aquí en adelante "medio de cultivo".

Procedimiento de ensayo:

Se cultivaron células THP-1 en matraces T-25cm^2 en medio de cultivo a 37°C, 5,0% de CO_2, 95% de aire hasta una densidad de células de 1x10^{6}células/ml Las células se cosecharon por centrifugación (5 minutos a 20G) y se resuspendieron en medio de cultivo modificado. Se realizó un conteo de células por exclusión con tintura azul Trypan y las células resultaron ser ≥ 90% viables. Las células se volvieron a centrifugar, se eliminó el sobrenadante, y el gránulo que se obtuvo se resuspendió hasta una concentración final de células de 1 x 10^6/0,1ml. Se fundió el reactivo de inclusión de células en agarosa y se puso en un baño de agua a 37°C. Se preparó la suspensión de células: se agregaron 0,15ml de las células THP-1 a un tubo de centrífuga de 1,5ml con 50µl de la solución fundida de agarosa. Adición a los recipientes-cápsulas: los recipientes-cápsulas se pusieron en una placa de microtítulo de 12 cavidades, se agregó un separador a la cápsula-recipiente, y se pipetearon 7µl de suspensión de células/agarosa en el centro del recipiente. Después de tres minutos, se pipeteó 1ml de medio de cultivo modificado al exterior de la cápsula-recipiente, y se pipetearon 200µl de

medio de cultivo modificado al interior Luego se puso el inserto de la cápsula dentro del recipiente con un fórceps estéril y se pipetearon 500µl de medio de cultivo modificado al interior del inserto Las cápsulas llenas se cargaron en las cámaras del microfisiómetro Las cámaras se perfundieron a una velocidad de 100µl/minuto con medio de cultivo modificado. El ciclo de bombeo fue de 50 segundos encendido y 40 segundos apagado. Se tomaron varios puntos de datos para representar la tasa metabólica y se utilizaron como línea de base. Las células se expusieron a los compuestos de la invención durante 30 minutos antes de la adición de agonistas de quimioquina a una concentración final de 10nM. Células tratadas y no tratadas se expusieron al agonista durante 100 segundos y se recogieron los datos

Al probarlos en este ensayo, los compuestos de la invención demostraron la capacidad de inhibir la activación del receptor CCR1 por MIP-1α o RANTES.

EJEMPLO 25

Ensayo *In vitro* para antagonistas del receptor CCR1.

Este ensayo demuestra las afinidades de los compuestos de la invención para unirse al receptor CCR1. Se determinaron las afinidades de unión de los compuestos por el receptor CCR1 en base a sus capacidades de competir con ^{125}I-MIP-1α o ^{125}I-RANTES por la unión al receptor CCR1

Reactivos y Soluciones. MIP-1α y RANTES (Peprotech Inc)

Células:

Se desprendieron células 293MR (K_D= 1-3nM y B_{max}= 2-3 x 10^6 sitios/célula) por tripsinización y se pusieron dentro de matraces por lo menos 48 horas antes del experimento.

Ligando:

Se reconstituyeron ^{125}I-MIP-1α y ^{125}I-RANTES de New England Nuclear (actividad específica de 2200Ci/mmol, 25μCi/vial) en 1ml de H_2O.

Solución amortiguadora de pH de ensayo:

NaCl 130mM, KCl 5mM, $MnCl_2$ 1mM, Tris 50mM, 30μg/ml de bacitracina, BSA 0,1%, pH 7,4

Solución amortiguadora de pH de lavado·

Solución amortiguadora de pH al fosfato (PBS)

Compuestos de la invención:

La solución madre de los compuestos era 1mM en DMSO al 100%. La concentración más alta en el ensayo fue 10μM y podía variar dependiendo de la potencia de los compuestos. Se hizo una dilución en series 1 3 desde la concentración más alta con solución amortiguadora de pH de ensayo. Usualmente se analizaron seis concentraciones de cada compuesto para generar una curva de dosis desde la cual se determinó el valor K_i.

Procedimiento de ensayo.

Los ensayos se llevaron a cabo en placas de microtítulo de 96 cavidades con fondo en V con un volumen total de

100µl.

Las células 293MR se desprendieron de los matraces T225cm^2 en PBS sacudiéndolos. Las células se lavaron una vez en PBS y se resuspendieron en la solución amortiguadora de pH de ensayo hasta aproximadamente 1,1 x 10^5 células/ml. Las células (aproximadamente 8000 células/ensayo) se incubaron tanto con ^{125}I-MIP-1α como con ^{125}I-RANTES (aproximadamente 15.000-20.000cpm/ensayo) en presencia y ausencia de diferentes concentraciones de los compuestos a temperatura ambiente durante 30-40 minutos

Las reacciones se hicieron terminar cosechando mediante una placa filtro GF/B remojada antes con PEI al 0,3% (Sigma # P- 3143) más BSA al 0,5% y lavando 5 veces con PBS frío. Las radioactividades en cada cavidad se determinaron por cuentas de centelleo después de agregar 50µl de fluido de centelleo.

La unión no específica se definió por la unión en presencia de MIP-1α o RANTES sin marcar 100nM. La concentración de receptor CCR1 que se utilizó en el ensayo fue ^{125}I-MIP-1α 0,4nM o ^{125}I-RANTES 0,06nM. Las concentraciones de los compuestos en el ensayo fueron típicamente entre 10µM y 30nM en dilución 1:3 y las concentraciones para los compuestos más potentes fueron menores, dependiendo de la potencia

Cálculos:

Se generaron las curvas de dosis de cada compuesto con

6 puntos de concentración y se determinaron los valores IC_{50} ajustando los datos a la ecuación log-logit (lineal) con una hoja de cálculo de EXCEL. Luego se calcularon los valores K_i dividiendo la IC_{50} por 1,025, para corregir la concentración de ligando marcado.

Cuando se probaron los compuestos de la invención en este ensayo, demostraron su afinidad para unirse al receptor CCR1.

Los datos que se dan en la tabla 2 muestran que los compuestos de la lista se unen a un receptor CCR1 y compiten con MIP-1α y RANTES. Los valores K_i están dentro del rango entre 1-172nM.

La tabla 2 es solamente una selección de los compuestos que se probaron.

En la tabla 1 se da una comparación con otros compuestos piperazina conocido. Los compuestos de acuerdo con la presente solicitud (No 10-12) tienen mayores afinidades de unión al receptor CCR1 que los compuestos alquilados en el carbono α (No 1-6, 13) y los compuestos que no está sustituidos sobre el anillo piperazina (No. 1-9). Por ejemplo los compuestos 1-6 tienen valores K_i mayor de 10μM.

Ejemplo 26

Se analizaron los efectos de un antagonista del CCR-1 sobre la migración/quimiotaxis celular en células U937 humanas y macrófagos peritoneales, aislados desde fluido perito-

neal proveniente de pacientes con endometrosis y controles.

La quimiotaxis se ensayó en cámaras Boyden que contenían membranas TEM permeables (Becton Dickinson, Franklin Lakes, NJ) con un tamaño de poro de 0,4µm de tereftalato de polietileno (P.E T.). En este ensayo, una línea celular histiocítica humana (U937) que se puede inducir para mostrar diferenciación monocítica y capacidad de respuesta quimiotáctica después del tratamiento con 8-bromo-adenosina monofosfato cíclico (cAMP) 1mM (Kay et al 1983)

Las células U937 se cultivaron a 37°C con 5% de CO_2 en medio RMPI suplementado con suero fetal bovino al 10% y penicilina G (100U/ml), estreptomicina (100µg/ml) y gentamicina (50µg/ml) y se incubaron con 8-bromo-cAMP 1mM (Sigma, St. Louis, MO) cada 24 horas durante un total de 48 horas. La presencia de proteína CCR-1 en las células U937 y macrófagos peritoneales se confirmó por análisis de transferencia Western· se sometieron 50µg de lisados de proteína de células U937 a SDS-PAGE y las proteínas se transfirieron a papel de nitrocelulosa según se describe en Hornung et al. 1997. Anticuerpos monoclonales IgG de ratón se cultivaron contra el receptor CCR-1 de RANTES humano.

Se preparó una mezcla de fluido peritoneal de 16 pacientes con endometrosis moderada o grave. La cantidad de proteína de RANTES se midió con ELISAs específicos (R&D Systems). Las muestras se diluyeron 1.4 en PBS con BSA al 0,1%

y se pusieron en el fondo de cavidades de las cámaras Boyden (600µl por cavidad). Luego se fijaron membranas TEM de P.E.T en su lugar en placas de 24 cavidades para separar compartimientos del fondo y superior y se agregaron 500.000 células en 200µl de PBS con BSA al 0,1% a las cavidades superiores. Antes de comenzar los experimentos, las células se preincubaron durante 30 min con antagonista del CCR1. Como control, las células se trataron con PBS. Las cámaras cargadas se incubaron a 37°C en aire humidificado con 5% de CO_2 durante 120 minutos. Las células que no migraron se eliminaron mediante varios lavados con PBS y las células que migraron se fijaron a la membrana con metanol absoluto durante toda la noche a 4°C y se tiñeron con Violeta Cristal (Sigma, St. Louis, MO). Se utilizó la absorción óptica a una longitud de onda de 570nm para cuantificar la quimiotaxis de los monocitos. La misma mezcla de fluido peritoneal se utilizó siempre como control positivo y los valores se normalizaron al 100% en cada conjunto de experimentos Como control negativo se utilizó siempre PBS solo.

Para evaluar el efecto inhibidor del antagonista del CCR-1, se utilizó la misma mezcla de fluido peritoneal de 16 pacientes con endometrosis moderada o grave. Se agregó el antagonista del CCR1 a concentraciones 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7} ó 10^{-6} molar.

ELISA de Apoptosis

Con formato

Se caracterizó la muerte celular programada por apoptosis por formación fragmentos genómicos de ADN de tamaño de multinucleosoma Los fragmentos de ADN son múltiplos de 180bp subunidades asociados con núcleos histonas. Se midieron los niveles de ADN liberado en el citosol de las células apoptósicas utilizando el conjunto de elementos de detección por ELISA de muerte celular (Roche, Mannheim, Alemania). El mismo es un cuantitativo inmunoensayo de unión a enzimas en sándwich que utiliza anticuerpos contra ADN e histonas. La el grado de fragmentación del ADN se expresa como un factor de enriquecimiento, que se calcula dividiendo la absorbancia de una muestra determinada por la absorbancia del correspondiente control de FCS al 10%

Evaluación de la apoptosis en células U937 tratadas con CCR-1

Un mecanismo potencial de inhibición de la quimiotaxis es mediante la apoptosis de monocitos Para excluir dicho mecanismo potencial, los inventores utilizaron un ELISA de fragmentación de ADN. Se cultivaron células U937 durante 24h en FCS al 10% (control) y al 2,5%. La muestra en FCS al 2,5% se incubó con antagonista del CCR-1 (ZK811752) Las células tratadas con TNF-alfa en FCS al 2,5% se utilizaron como control positivo.

Análisis estadísticos

Todos los experimentos se repitieron tres veces y los

resultados se expresaron como el promedio ± SD. Los datos con distribución normal se analizaron por test t pareado o ANOVA. Los datos no paramétricos se analizaron mediante las estadísticas de Kruskal-Wallis y Mann-Whitney. Se aceptaron diferencias significativas cuando el análisis de dos colas dio P< 0,05.

Ejemplo 27

Determinación del mARN de CCR1 en muestra de tejido endometrial y endometriósico por análisis cuantitativo RT-PCR en tiempo real.

Se extrajo ARN total del endometrio y lesiones endometriósicas utilizando Reactivo Trizol (Life Technologies, cat. no: 15596-026). Después se utilizaron 20µg de ARN total para enriquecer poli (A) +RNA (Medcalf et al., EMBO. J. 1986; 5, 2217).

La síntesis de cADN se realizó utilizando un sistema de síntesis SuperScript First-Strand (Invitrogen) La cuantificación de la abundancia de mARN se realizó mediante detección por PCR en tiempo real utilizando un sistema de detección de secuencias ABI PRISM 7700 (PE Biosystems, Inc., Weiterstadt, Alemania) y SYBRGreen como tintura fluorescente específica para ADN de doble hebra (SYBRGreen PCR Master MIX, PE Biosystems). Par la cuantificación de transcripciones amplificadas, se utilizaron 0,2µl de cADN de la primera hebra. La cuantificación relativa de los datos del sistema

de detección de secuencia ABI PRISM 7700 se realizó utilizando el método CT comparativo.

Primer par específico para detección de CCR1: 5`-CTC-CGT-GCC-AGA-AGG-TGA-AC-3´ y 5`-CCA-GGA-CCA-CCA-GGA-TGT-TT-3´. El control interno y gen de referencia fue el gen doméstico de ciclofilina (Primer par· 5'-GAA-GTT-GGC-CGC-ATG-AAG-A-3' y 5'-GCC-TAA-AGT-TCT-CGG-CCG-T-3'). Reacción PCR: 10 min 95°C, 15 seg 95°C, 1 min 62°C (40 ciclos). La pureza de los productos de la amplificación se controló por curvas de fusión.

Ejemplo 28

Análisis inmunohistoquímico del CCR1 en lesiones endometriósicas y en el endometrio Se congelaron las biopsias en el punto de recolección y se almacenaron a -80°C. Para cortarlos, los tejidos se incluyeron primero en TissueTek (Sakura) y se equilibraron a -20°C Antes de la inmunotinción,las placas congeladas se descongelaron y se secaron al aire durante 2 horas a temperatura ambiente.

Para el análisis inmunohistoquímico luego se cortaron las secciones de tejido utilizando un Leica Kryotome y se montaron sobre placas de vidrio SuperFrost Plus. Se realizaron las criosecciones de 5µm y se fijaron durante 10 min en acetona a 4°C Las criosecciones fijadas se lavaron en TBS y se bloquearon con solución de bloqueo de peroxidasa (DAKO). Después de otro procedimiento de lavado, las placas de teji-

do se bloquearon durante 15 min con solución de bloqueo de proteínas de DAKO

El tejido proveniente de lesiones peritoneales y del endometrio se incubó durante 30 min con un anticuerpo monoclonal para CCR1 (clone 53504.111, R&D Systems) con una concentración de 0,8µg/ml. La tinción inmunohistoquímica se llevó a cabo con Conjunto de elementos cabra anti-ratón DAKO EnVision System, Peroxidasa (AEC) (DAKO: K4004). Las muestras se lavaron y se incubaron con EnVision-Sistema polímero marcado con peroxidasa (DAKO) Después de 15 min de incubación con AEC-Chromogen las muestras se lavaron y se incubaron durante 5 min en hematoxilina. Los tejidos teñidos se incluyeron en Fluoromount G (Dunn Labortechnik GmbH). Para la caracterización de las células inmunes que expresan el CCR1, las muestras se tiñeron con anticuerpos para CD4/CD14 y CD68 (Dako) y Alexa 568 (Sondas moleculares). Los tejidos teñidos se examinaron con un microscopio Axioplan por imágenes. Se tomaron fotografías con el sistema de cámara AxioCam, Axiovision 3.1, KS400 (Carl Zeiss) Todas las imágenes se tomaron con el mismo tiempo de exposición.

Ejemplo 29

Efectos de los compuestos de acuerdo con la presente invención sobre la endometrosis inducida quirúrgicamente en ratas intactas que atraviesan un ciclo

Procedimiento quirúrgico: La endometrosis se indujo

quirúrgicamente en ratas Wistar hembra (200g-250g de peso corporal) con un ciclo menstrual normal de 4 días. Todos los procedimientos se llevaron a cabo en condiciones estériles. Durante la primera laparotomía, se hizo una resección de una porción de 2cm de la trompa uterina derecha y se puso en PBS a 37°C. El segmento uterino se abrió longitudinalmente, y se peló el endometrio para separarlo del miometrio. Se transplantó un segmento al peritoneo parietal de la pared abdominal derecha y el otro segmento a las cascadas arteriales del mesenterio intestinal. Los segmentos se suturaron utilizando sutura de seda no absorbible en cuatro esquinas, con la superficie del endometrio hacia el lumen de la cavidad peritoneal. Cuatro semanas después de la inducción de la endometrosis, los animales sufrieron una segunda laparotomía para evaluar el tamaño y la viabilidad del tejido ectópico endometrial. Macroscópicamente, dicha laparotomía reveló la formación de estructuras quísticas (focos similares a la endometrosis) en el ~90% de los animales Se midió el área superficial en longitud X ancho (mm^2) utilizando un calibre. Para el experimento se utilizaron solamente animales donde el endometrio ectópico había formado focos similares a la endometrosis en ambas posiciones. Los animales se dividieron en 4 grupos (n= 10 animales por grupo). Los animales del grupo 1 (controles) recibieron solamente vehículo. Los animales del grupo 2 se trataron con un antiestrógeno (referen-

cia de control positivo) (dosis 1mg/kg) diaria. Los del grupo 3 recibieron 50mg/kg con (2R)-1-{[4-cloro-2-(ureido)fenoxi]metil}carbonil-2-metil-4-(4-fluorobencil)piperazina como sal cloruro dos veces al día. A los animales del grupo 4 se les hizo una operación ficticia. Los grupos 1-3 se trataron con inyecciones s c. diarias durante 4 semanas

Evaluación: Los animales se sacrificaron con una atmósfera de CO_2 después de 4 semanas de tratamiento Durante la autopsia, se calculó el número de animales con lesiones endometriósicas persistentes o sin ellas y se midió *in situ* el área superficial y el volumen La expresión del mARN del CCR1 y RANTES en útero, ovarios, quistes endometriósicos peritoneales y mesenteriales de rata se analizó y se cuantificó según se describe en el ejemplo 27.

Ejemplo 30

Se indujo experimentalmente la endometrosis por inoculación de endometrio menstrual o por transplante autólogo según se describe en la literatura(11, 12, 13, 14).El análisis inmunohistoquímico del CCR1 en injertos/lesiones endometriósicos se llevó a cabo según se describe en el ejemplo 28.

Primera parte del estudio· Tratamiento de la endometrosis. Después de inducir la endometrosis, se trataron primates con diferentes concentraciones del antagonista del CCR1

durante 2-3 semanas Como control, los animales se trataron con vehículo, antagonista de GnRH y placebo Se llevó a cabo una videolaparoscopía para documentar el número, superficie, volumen y puntaje revisado de la American Fertility Society (rAFS) y etapa de las lesiones endometriósicas. Todas las laparoscopías las realizó un único investigador. Se tomaron y analizaron muestras de suero y sangre antes de inducir la enfermedad y durante el tratamiento. En la segunda parte del estudio, los animales se trataron con antagonista del CCR1 antes de inducir la endometrosis, en particular con (2R)-1-{[4-cloro-2-(ureido)fenoxi]metil}carbonil-2-metil-4-(4-fluorobencil)piperazina como sal sulfato. Al terminar el estudio, las lesiones endometriósicas se sometieron a un análisis inmunohistoquímico y análisis molecular biológico.

Ejemplo 31

Eficacia del antagonista del CCR1 de acuerdo con la invención en el tratamiento de la endometrosis sintomática.

El siguiente estudio clínico se llevó a cabo para evaluar la eficacia de los antagonistas del CCR-1 de acuerdo con la invención, en particular (2R)-1-{[4-cloro-2-(ureido)fenoxi]metil}carbonil-2-metil-4-(4-fluorobencil)piperazina como sal sulfato, para el tratamiento de la endometrosis y del dolor pélvico asociado.

Se diseñó un estudio multicentro, controlado con placebo, al azar, doble ciego en grupos paralelos con una pobla-

ción de mujeres jóvenes fértiles con endometrosis históricamente confirmada a la edad de 18-45 años, con infertilidad o sin ella

El estudio fue controlado con placebo, al azar, de doble ciego en grupos paralelos. La duración del tratamiento fue de tres meses.

La variable de eficacia primaria es el cambio del dolor pélvico según una escala visual análoga. Variables de eficacia secundarias: Reducción de absorción de co-medicación para el dolor pélvico. Parámetros de seguridad· El examen físico y ginecológico incluyó mamas, seguridad en laboratorio, patrones de hemorragia (diario de la paciente).

La invención se acaba de describir con referencia a las formas preferidas de realización Sin embargo queda claro que la invención es susceptible de numerosas variaciones dentro de la doctrina de los equivalentes técnicos.

Bibliografía citada

1. Neote, K., DiGregorio, D., Mak, J.Y , Horuk, R., and Schall, T.J 1993. Molecular cloning, functional expression, and signaling characteristics of a C-C chemokine receptor. Cell 72.415-425.

2 Su, S.B., Mukaida, N., Wang, J , Nomura, H., and Matsushima, K. 1996. Preparation of specific polyclonal antibodies to a C-C chemokine receptor, CCR1, and determination of CCR1 expression on various types of leukocytes. J Leukoc

Biol 60:658-666.

3. Hornung, D., Ryan, I.P., Chao, V.A., Vigne, J.L., Schriock, E D., and Taylor, R N. 1997. Immunolocalization and regulation of the chemokine RANTES in human endometrial and endometrosis tissues and cells J Clin Endocrinol Metab 82.1621-1628.

4. Khorram, O., Taylor, R N., Ryan, I P., Schall, T.J., and Landers, D.V. 1993. Peritoneal fluid concentrations of the cytokine RANTES correlate with the severity of endometrosis. Am J Obstet Gynecol 169:1545-1549.

5. Hornung, D , Bentzien, F., Wallwiener, D , Kiesel, L., and Taylor, R.N. 2001. Chemokine bioactivity of RANTES in endometriotic and normal endometrial stromal cells and peritoneal fluid Mol Hum Reprod 7·163-168.

6. Zhao, D., Lebovic, D.I., and Taylor, R.N 2002. Long-term progestin treatment inhibits RANTES (regulated on activation, normal T cell expressed and secreted) gene expression in human endometrial stromal cells J Clin Endocrinol Metab 87:2514-2519

7. Altman, G.B., Gown, A.M , Luchtel, D.L., and Baker, C. 1999. RANTES production by cultured primate endometrial epithelial cells. Am J Reprod Immunol 42:168-174.

Cheret A., Le Grand R., Caufour P., Neildez O., Matheux F., Theodoro F.,

8. Medcalf R.L., Richards R.I., Crawford R J. and Hamil-

ton J.A.1986. Suppression of urokinase-type plasminogen activator mRNA levels in human fibrosarcoma cells and synovial fibroblasts by anti-inflammatory glucocorticoids. EMBO J. 5(9), 2217-22

9. Vaslin B , Dormont D. RANTES, IFN-gamma, CCR1, and CCR5 mRNA expression in peripheral blood, lymph node, and bronchoalveolar lavage mononuclear cells during primary simian immunodeficiency virus infection of macaques. 1999. Virology. 15;255(2):285-93.

10. Margulies B.J., Hauer D.A , Clements J.E. Identification and comparison of eleven rhesus macaque chemokine receptors 2001 AIDS Res Hum Retroviruses. 1,17(10) 981-6.

11 D'Hooghe T M , Bambra C.S., Raeymaekers B.M., De Jonge I., Lauweryns J.M., Koninckx P R Intrapelvic injection of menstrual endometrium causes endometrosis in baboons (Papio cynocephalus and Papio anubis).1995 Am J Obstet Gynecol.173(1):125-34.

12 Zong L.L., Li Y L., Wang L X , Zou J., Li J., Li T. Di Yi Jun Yi Da Xue Xue Bao. Establishment of animal models of endometrosis in rhesus monkeys.2003.23(10):1006-9.

13 D'Hooghe T.M , Nugent N., Cuneo, S., Chai D , Deer, F., Debrock, S. Mwenda, J (2001).Recombinant human TNF binding protein (r-hTBP-1) inhibits the development of endometrosis in baboons: a prospective, randomized, placebo-and drug-controlled study.Abstract for an oral presentation at

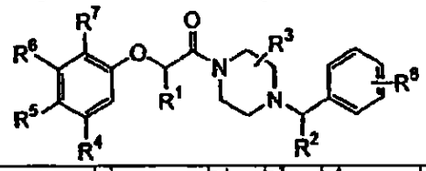
the Annual Meeting of the American Socity for Reproductive Medecine, Orlando, USA October 22nd-24th.

14 Fazleabas A.T., Brudney A., Gurates B., Chai D., Bulun S. 2002. A modified baboon model for endometrosis Ann N Y Acad Sci. 955: 308-317; discussion 340-2, 396-406.

15 Stoeckemann K., Hegele-Hartung C. Effects of progesterone antagonists onapristone and ZK 136799 on surgically induced endometrosis in intact cycling rats.Human Reproduction 1995 Dec, 10(12): 3264-71

TABLA I

Compuestos de ensayo



Comp Nro	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Ki (nM)
1	metilo	H	H	metoxi	metoxi	metoxi	H	H	> 10μM
2	etilo	H	H	metoxi	metoxi	metoxi	H	H	> 10μM
3	isopropilo	H	H	metoxi	metoxi	metoxi	H	H	> 10μM
4	propilo	H	H	metoxi	metoxi	metoxi	H	H	> 10μM
5	butilo	H	H	metoxi	metoxi	metoxi	H	H	> 10μM
6	hexilo	H	H	metoxi	metoxi	metoxi	H	H	> 10μM
7	H	H	H	metoxi	metoxi	metoxi	H	H	328 nM
8	H	H	H	metoxi	H	H	H	H	> 10μM
9	H	H	H	H	metoxi	H	H	H	> 10μM
10	H	H	metilo	metoxi	metoxi	metoxi	H	F	18 nM
11	H	H	me-	H	Cl	H	H	F	10 nM

725

			tilo						
12	H	H	2,5-dimetilo	H	Cl	H	H	F	4 nM
13	dimetilo	H	metilo	H	Cl	H	H	F	> 10μM

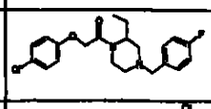
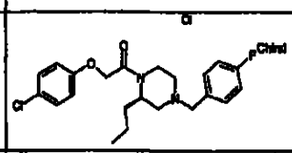
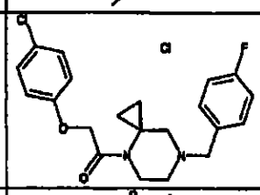
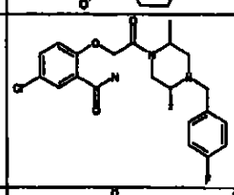
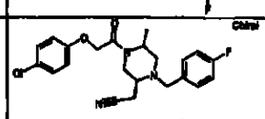
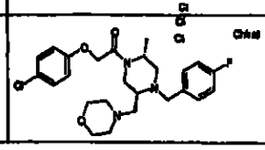
TABLA II

Nro	Compuesto	Ki⁻(nM)
1	1((fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina	108
2	(trans)-1-((4-clorofenilamino)metil)carbonil-2,5dimetil-4-(4-fluorobencil)piperazina	16
3	(trans)-1-((4-cloro-3-nitrofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina	11
4	(trans)-1-((4-cloro-2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	56
5	(trans)-1-((4-cloro-2-(dietilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	32
6	(mtrans)-1-((4-cloro-2-hidroxifenoxi)metil)carbonil-2,5dimetit-4-(4fluorobencil)piperazina	11
7	(trans)-1-((4-cloro-2-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-flulorobencil)piperazina	10
8	(trans)-1-((5-chloro-2-metoxifenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	15
9	1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2-metil-4-(4-fuorobencil)piperazina	3
10	(2R,5S)-1-((4-cloro-3-(hidroximetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	3
11	(trans)-1-((4-cloro-2-(1-hidroxietil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	5

12	(trans)-1-((4-cloro-2-(aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	5
13	(trans)-1-((4-cloro-2-((etil)(1-metilbutil)aminometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	41
14	(trans)-1-((4-cloro-2-(ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	2
15	1-((4-cloro-2-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	9
16	1-((4-cloro-3-nitrofenoxi)metil)carbonil-2-metil-4-(4fluorobencil)piperazina	21
17	(trans)-1-((4-cloro-2-(bencilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	42
18	(trans)-1-((4-cloro-2-((1-metilbutil)amino)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	87
19	1-((4-cloro-2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina	5
20	(trans)-1-((4-cloro-2-(propilcarbonilamino)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	7
21	(trans)-1-((4-cloro-2-(iso-propilcarbonilamino)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	13
22	(trans)-1-((4-cloro-2-(metoximetilcarbonilamino)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	3
23	(trans)-1-((4-cloro-2-(2-(metoxicarbonil)etilcarbonilamino)-fenoxi)-metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	5
24	(trans)-1-((4-cloro-2-(metilsulfonilamino)fenoxi}metil)carbonlil-2,5-dimetil-4-(4-fuorobencil)piperazina	6
25	(2S)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fuorobencil)piperazina	1

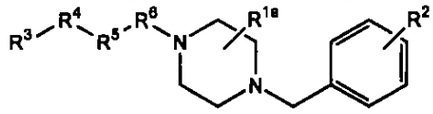
26	(trans)-1-((4-cloro-2-(glicinamida)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	1
27	(trans)-1-4-cloro-2-((aminocarbonil)glicinamido-fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	2
28	(trans)-1-((4-cloro-2-(1-((metil)(etil)amino)etil)feno-xi)-metil)carbonil-2,5 -dimetil-4-(4-fluorobencil)piperazina	18
29	(trans)-1-((-4-cloro-2-(1-(imidazol-1-il)etil)feno-xi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	6
30	(trans)-1-((4-cloro-2-((2-aminoetil)aminocarbonil)feno-xi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)pipe-razina	9
31	1-((2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina	106
32	(trans)-1-((3-cianofenoxi)metiI)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	68
33	(2R,5S)-1-((3-hidroxi-5-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	5
34	(trans)-1-((5-metoxi-2-(metoxicarbonil)fenoxi)me-til)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	31
35	1-((4-clorofenoxi)metil)carbonil-2-(1-hidroxietil)-4-(4-fluorobencil)piperazina	13
36	1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxibut-3-enil)-4-(4-fluorobenzil)piperazina	172
37	1((4-clorofenoxi)metilcarbonil-3-trifluorometil-4-(4-fluorobencil)piperazina	148
38	1-((4-clorofenoxi)metil)carbonil-2-(azidoetil)-4-(4-fluorobencil)piperazina	49
39	*(trans)-1-((benzo*[b]pyran-2-on-7-iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	*18*
40	(trans)-1-((4-cloro-2-(ftalimido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	64
41	(trans)-1-(2-(4-clorofenil)-3-(amino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	56

42	(trans)-1-(2-(4-clorofenil)-3-(acetilamino)propil)carboril-2,5-dimetil-4-(4-fluorobencil)piperazina	26
43	(trans)-1-(2-(4-clorofenil)-2-(metilsulfonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina	32

No	Compuesto	Ki (nM)
44		15
45		75
46		74
47		3
48		38
49		109

REIVINDICACIONES

1. Uso de un compuesto de la siguiente fórmula (Ia):



(Ia)

en la producción de un medicamento para el tratamiento y la prevención de la endometrosis en seres humanos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por oxo, halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, ((C3-C10)cicloalquil(C1-C8)alquil) amino(C1-C8)alquilo, halo(C1-C8)alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2- C8)alquenilo, formilo, formil(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidroxi(C2- C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (hidroxi)(C3-C10)cicloalquil(C1-C8)alquilo, mercapto(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo op-

cionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8) alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8) alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, azido(C1-C8)alquilo, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8) alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8) alquilo, (C1-C8)alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sus-

tituido)(C1-C8) alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo

formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto, mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsufonilo, (C1- C8)alquiltio(C1-C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8) alquilsulfonil(C1-C8)alquilo, (C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi, halo(C1-C8) alcoxi, (C3-C10)cicloalquilo, (C3-C10)cicloalquil(C1-C8)alquilo, (hidroxi)(C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino, (C3-C10) cicloalquilamino(C1-C8)alquilo, ((C3-C10)cicloalquil(C1-C8)alquil)amino, ((C3-C10)cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, ciano(C1-C8)alquilo, (C2-C8) alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2-C8)alquenilo, hidroxi(C1-C8)alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8) alquinilo, (C1-C8)alcoxi(C1-C8)alquilo, ((C1-C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-

C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1- C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8) alquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino, ((C1-C8) alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8)alcoxicarbonilamino(C1-C8) alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcox-icarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxicarbonilo, (C1-C8)alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)al-

quilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbony((C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1- C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C7-C8) alquilaminocarbonil(C1-C8)alquilo, amidino, guanidino, ureido, mono(C1-C8) alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (3- 15 membered heterociclilo que consiste de átomos de

carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^3 es

un sistema de anillo carbocíclico de 3 a 15 miembros sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto, mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsufonilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, (C1-C8)alquiltio(C1- C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8) alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi, halo(C1-C8)alcoxi, amino(C1-C8)alcoxi, (C3-C10)cicloalquilo, (C3- C10)cicloalquil(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, (C3- C10)cicloalquilamino, (C3-C10)cicloalquilamino(C1-C8)alquilo, ciano(C1-C8) alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo

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o naftilo opcionalmente sustituido)(C2-C8) alquenilo, hidroxi(C1-C8)alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (hidroxi(C1-C8)alquil)tio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (C1-C8)alcoxi(C1-C8)alquilo, ((C1-C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1- C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, amino(C1-C8)alquilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino, ((C3-C10) cicloalquil(C1-C8)alquil)amino, alquilcarbonilamino, (C1-C8) alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos

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seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, ((C1-C8) alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8)alquilsulfonilamino, amino(C1- C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8) alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1- C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, ((C3-C10) cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente susti-

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tuido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonyt(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, di(C1-C8) alquilaminocarboniloxi(C1-C8)alquilo, (C1-C8)alquilcarbonil(C1-C8)al-quilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8) alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (mono(C1-C8) alquilaminocarbonil(C1-C8)al-

quil)aminocarbonilo, (carboxi(C1-C8)alquil) aminocarbonilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, amidino, hidroxiamidino, guanidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, monohalo(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, di(C1-C8)alquilureido, di(fenilo o naftilo opcionalmente sustituido)ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureidoalquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbo-

nil(C1-C8)alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, glicinamido(C1-C8)alquilo, alaninamido, mono(C1-C8) alquilalaninamido, alaninamido(C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por

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nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

o R^3 es

un sistema de anillo heterocíclico de 3-15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alquilsufonilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, (C1-C8)alcoxi, hidroxi(C1-C8) alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, halo(C1-C8)alcoxi, (C2-C8) alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, amino, mono(C1- C8) alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8) alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil(C1-C8) alquil)amino, ((C1-C8)al-

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coxicarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, monoalquilamino(C1-C8)alquilo, di(C1- C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8) alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, guanidino, ureido, mono(C1- C8) alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, y glicinamido;

R^4 es

-O-, $-N(R^7)-$, $-C(R^8)_2-$ o un enlace;

R^5 es

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una cadena (C1-C8) alquileno o una cadena (C1-C8) alquilideno, o, si R^4 es un enlace, R^5 es una cadena (C1-C8) alquilideno que se sustituye opcionalmente por (fenilo o naftilo opcionalmente sustituido) o -$N(R^7)_2$;

o R^4 y R^5 juntos son -HC=CH-

R^6 es

-C(O)-, -C(S)-, $-CH_2-$ o un enlace;

cada R^7

se selecciona en forma independiente entre el grupo formado por hidrógeno, (C1- C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alquilcarbonilo, (C1-C8) alquilcarbonil(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)(C1- C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8)alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi, (C1-C8)alcoxi, hidro-

xi(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8) alquilamino, di(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8) alquilcarbonil)((C1-C8)alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, cicloalquilcarbonilamino(C1-C8)alquilo, (C1- C8)alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) aminoalquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-

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C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1- C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, carboxi(C1-C8) alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, y di(C1-C8) alquilaminocarbonil(C1-C8)alquilo;

con la salvedad de que cuando R^4 es $-N(R^7)-$, R^3 no puede ser un sistema de anillo heterocíclico que contiene entre 4 y 8 miembros que consiste de átomos de carbono y sólo un átomo de nitrógeno; y con la salvedad de que cuando R^4 es $-C(R^8)_2$ o un enlace, R^3 no puede ser un sistema de anillo heterocíclico saturado con puente de 4-6 miembros que consiste de átomos de carbono y dos átomos de nitrógeno, y como único estereoisómero o una mezcla de los mismos; o una sal aceptable para uso farmacéutico de los mismos.

2. El compuesto de la reivindicación 1 en el que:

R^3 es

un sistema de anillo carbocíclico de 3 a 15 miembros sustituido por uno o más sustituyentes seleccionados

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entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto, mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsulfonilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, (C1-C8)alquiltio(C1- C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8) alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi, halo(C1-C8)alcoxi, amino(C1-C8)alcoxi, (C3-C10)cicloalquilo, (C3- C10)cicloalquil(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, (C3- C10)cicloalquilamino, (C3-C10)cicloalquilamino(C1-C8)alquilo, ciano(C1-C8) alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2-C8)alquenilo, hidroxi(C1-C8) alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (hidroxi(C1-C8)alquil)tio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hi-

droxi(C2-C8)alquinilo, (C1-C8)alcoxi(C1-C8)alquilo, ((C1-C8)alcoxi) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8) alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, amino(C1-C8)alquilamino, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, amino, ((C3-C10)cicloalquil(C1- C8)alquil) amino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil) ((C1-C8)alquil)amino, ((C1-C8)alcoxicarbonil)((C1-C8)al-

quil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8) alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alco-

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xicarbonilo, (C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, di(C1-C8) alquilaminocarboniloxi(C1-C8)alquilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8) alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (mono(C1-C8) alquilaminocarbonil(C1-C8)alquil)aminocarbonilo, (carboxi(C1-C8)alquil) aminocarbonilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o

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naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, amidino, hidroxiamidino, guanidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, monohalo(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, di(C1-C8)alquilureido, di(fenilo o naftilo opcionalmente sustituido)ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido (C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glici-

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namido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, glicinamido(C1-C8)alquilo, alaninamido, mono(C1-C8) alquilalaninamido, alaninamido (C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo.

3. El compuesto de la reivindicación 2 en el que:

R^4 es

-O-, $-N(R^7)-$ o $-C(R^8)-$;

R^5 es

una cadena (C1-C8) alquileno;

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R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1- C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10)cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8)alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcar-bonil)((C1-C8)alquil)amino, (fenilo o naftilo

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opcionalmente sustituido)(C1-C8)alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8) alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil) ((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8)alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8) alquilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil4(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo,

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mono(C1-C8)alquilamlnocarbonil(C1-C8)alquilo, y di(C1-C8)alquilaminocarbonil(C1-C8)alquilo.

4. El compuesto de la reivindicación 3 en el que:

R^4 es

-O-,

R^5 es

metileno; y

R^6 es

-C(O)-

5 El compuesto de la reivindicación 4, en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8) alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2- C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, ciano(C1-C8)alquilo, halo(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1- C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8)alquilo, hidroxi(C1-C8) alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcional-

mente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterocíclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo,

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)al-

quilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8) alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1- C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquil-carbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcar-

bonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-CS)alcoxicarbonilamino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8) alcoxi) carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil) aminocarbonilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido) ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilurei-

do, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mo-

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no(fenilo o naftilo opcionalmente sustituido)amino-carbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, y (3- 15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

6 El compuesto de la reivindicación 5 seleccionado del grupo formado por los siguientes compuestos·

(2*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((fenoxi)metil)carbonil-2-etil-4-(4-fluorobencil)piperazina,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina,

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(metoximetil) piperazina,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-((acetilamino)metil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((4-fluorobencil)amino)etil)-4-(4-fluorobencil) piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((metil)amino)etil)-4- (4-fluorobencil)piperazina;

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1-((4-clorofenoxı)metıl)carbonil-2-(2-((2-hıdroxı-etıl)amıno)etıl)-4-(4-fluorobencıl)pıperazina;

4-(4-fluorobencıl)-1-((4-clorofenoxı)metıl)carbonıl-3-((((4-clorofenoxı)metıl)carbonıl)oxı)metıl-5-metılpıperazına;

4- (4-fluorobencıl)-1-((4-clorofenoxi)metıl)carbonıl-3-(etoxıcarbonıl) pıperazına,

4-(4-fluorobencıl)-1-((4-clorofenoxı)metıl) carbonıl-3-(metoxicarbonil)metılpıperazına;

4-(4-fluorobencıl)- 1-((4-clorofenoxi)metıl)carbonıl-3-((metoxı)metıl)pıperazına,

4-(4-fluorobencıl)-1-((4-clorofenoxı)metıl)carbonıl-3-(2-(metoxı) etıl)pıperazına,

4-(4-fluorobencıl)-1-((4-clorofenoxi)metıl) carbonıl-3-(2-hidroxi-2-(4-metılfenıl)etıl)pıperazına;

4-(4- fluorobencıl)-1-((4-clorofenoxı)metıl)carbonıl-3-(2-hıdroxıpropıl) pıperazına;

4-(4-fluorobencıl)-1-((4-clorofenoxı)metil) carbonıl-3-(2-hidroxıbut-4-ınıl)pıperazına;

4-(4-fluorobencıl)-1-((4-clorofenoxi)metıl)carbonıl-5-(2-hıdroxı-2-metılpropıl)pıperazina,

4-(4-fluorobencıl)-1-((4-clorofenoxı)metıl)carbonıl-3-(2- hıdroxıetıl)pıperazına ;

1-((4-clorofenoxı)metıl)carbonıl-3-(2-((2-hıdroxi-etıl)amino)etil)-4-(4-fluorobencil)piperazına;

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(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,3- dimetilpiperazina;

(2*S*,5*R*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-(2-metiltio)etilpiperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5- (benciloxi)metilpiperazina;

(2*R*,5*R*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-(((2-hidroxietil)tio)metil)piperazina;

4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-2-(*N'*-(etoxicarbonilmetil) ureido) metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((amino)carboniloxi)metil-4-(4-fluorobencil) piperazina,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-((acetil)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1-hidroxi-1-(fenil)metil)piperazina,

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-metil-5-(1-hidroxibutil)piperazina;

(2*R*,5 *S*)-1-((4-clorofenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)-5-((dıetılamıno)metıl)pıperazına;

(2*R*,5*S*)-1-((4- clorofenoxi)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)-5-((dimetilamino)metıl)pıperazına;

(2*R*,5*S*)-1-((4- clorofenoxı)metil)carbonil-2-metil-4-(4-fluorobencıl)-5- ((cıclopropıl)amıno)metıl)pıperazına;

(2*R*,5*S*)-1-((4-clorofenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)-5 ((morfolın-4-ıl)metil)piperazina;

(2*R*,5*R*)-1-((4- clorofenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)-5-((pıperazın-1- ıl)metil)piperazina;

(*cıs*)-1-((3,4,5-trimetoxifenoxı)metıl)carbonil-2,6-dimetıl-4-(4-fluorobencıl)pıperazına;

(*cıs*)-4-(4-fluorobencıl)-1-((4-clorofenoxı)me-tıl)carbonıl-2,6- dımetılpıperazına;

1-((fenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)pıperazina,

1-((2-(acetılamıno)fenoxı)metıl)carbonıl-2-metil-4-(4-fluorobencıl)pıperazına;

1-((4- clorofenoxı)metıl)carbonıl-2-(2-hıdroxıpropil)-4-(4-fluorobencil) piperazına;

1-((4-clorofenoxı)metıl)carbonıl-2-(2-hıdroxıbut-3-enıl)-4-(4-fluorobencil)pıperazına;

1-((4-clorofenoxı)metil) carbonıl-3-trıfluorometıl-4-(4-fluorobencıl)piperazına; y

(*trans*)-1-((4-cloro-2-((4-(2,5-di(trifluorometil)fenilcarbonil)piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina.

7. El compuesto de la reivindicación 5, en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8)alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8) alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10)cicloalquilamino(C1-

C8)alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3- C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbo-nilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilami-

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no(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1- C8)alquil)((C1-C8)alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicar-

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bonil(C1-C8) alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8) alquilcarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1- C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo.

8 El compuesto de la reivindicación 7 seleccionado del grupo formado por los siguientes compuestos:

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1-((3,4,5-trimetoxifenoxi)metil)carbonil-2- metil-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina;

(2*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- propilpiperazina;

(2*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-propilpiperazina,

4-(4-fluorobencil)-1-(((4-clorofenoxi)metil)carbonil)espiro[ciclopropan-1, 2'-piperazina];

1-((4-clorofenoxi)metil)carbonil-2- hidroximetil-4-(4-fluorobencil)piperazina,

4-(4-fluorobencil)-1- ((4-clorofenoxi)metil)carbonil-2-(2-(metoxi)etil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-metilpropil)amino)etil) -4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

1-((4- clorofenoxi)metil)carbonil-4-(4-fluorobencil)-5-metilpiperazina;

(2*R*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

(2*S*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-

fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(hidroximetil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxietil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(((metil)ureido)metil)piperazina;

(2*R*,3*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2,3-dimetilpiperazina;

(*cis*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetil-4-(4-fluorobencil)piperazina,

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-(((4-clorofenoxi)metil)carbonil)oxi)etil-5-metilpiperazina;

(2 *R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5((hidroxi)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((metoxi)-metil)piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-metil-5-(1-metiletil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-(1-hidroxietil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1- hidroxiprop-3-enil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-

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fluorobencıl)-5-((cıano) metıl)pıperazına;

(2*R*,5*R*)-1-((4-clorofenoxı) metıl)carbonıl-2-metıl-4-(4-fluorobencıl)-5-((1,2,4-trıazol-2-ıl)metıl) pıperazına;

(2*R*,5*R*)-1-((4-clorofenoxı)metıl) carbonıl-2-metıl-4-(4-fluorobencıl)-5-((tetrazolıl)metıl)pıperazına;

(3*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3,5-dimetılpiperazına;

1-((4-cloro-3- nıtrofenoxi)metil)carbonıl-2-metıl-4-(4-fluorobencıl)pıperazına,

(*trans*)-1-((4-cloro-2-metilfenoxı)metıl)carbonıl-2,5-dimetil-4-(4-fluorobencil)piperazına;

(*trans*)-1-((4-cloro-2-(dıetılamıno)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4- fluorobencıl)pıperazina;

(*trans*)-1-((4-cloro-2-hıdroxıfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazina;

(*trans*)-1-((5-cloro-2-metoxıfenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((etıl)(1-metılbutıl)amınometıl)fenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencil)piperazina,

1-((4-cloro-2- amınofenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl)pıperazına,

1-((4-cloro-3-nitrofenoxi)metıl)carbonıl-2-metil-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-(bencilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((1-metilbutil)amino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*iso*-propilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diclorofenil)ureido)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(4-nitrofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(4-metilfenil)ureido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-bencilureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((ciclopropilmetil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(fenilaminometil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(acetilaminometil)fenoxi)metil)

carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((metilamino)(fenil)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(fenilsulfonil)(metil) aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(acetil)(metil)aminoetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina,

(*trans*)-1-((4-cloro-2-(1-(*N*-metil- *N'*-etilureido)etil) fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1- ((metil)(etil)amino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(dimetilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)-1-((4-cloro-2-((4-*t*- butoxicarbonilpiperazin-1-il)metil)fenoxi)metil)carbonil-2-metil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(oxazol-2- ılamınometil)fenoxi) metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil) piperazına,

1-((4-cloro-2-(morfolın-4-ilmetıl)fenoxı)metıl) carbonıl-2-metıl-4-(4-fluorobencıl)pıperazına;

(trans)-1- ((4-bromo-2-formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(*trans*)-1-((4-fluoro-3-clorofenoxı)metil) carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

1-((4-cloro-2-metoxıcarbonılfenoxı)metıl)carbonıl-2-metıl-4-(4-fluorobencıl) pıperazına;

(*trans*)-1-((4-cloro-2-metoxıcarbonılfenoxı) metıl) carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

1-((4-cloro-2-amınocarbonılfenoxı)metıl)carbonıl-2-metil-4-(4-fluorobencil) piperazına;

(*trans*)-1-((4-cloro-2-carboxıfenoxı)metil) carbonil-2,5-dımetıl-4-(4-fluorobencil)pıperazına;

(*trans*)-1-((4-cloro-2-formılfenoxı)metil)carbonıl-2,5-dimetil-4-(4- fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-cianofenoxı)metıl)carbonil-2,5-dimetıl-4-(4-fluorobencil)piperazına;

(*trans)*-1-((3-cıanofenoxi)metıl)carbonıl-2,5-dimetil-4-(4-fluorobencıl)pıperazına,

(*trans*)-1-((4-metıl-2-amınofenoxı)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazına;

(*trans*)-1-((3-formılfenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencil)pıperazına,

(*trans*)-1-((4-metıl-2-acetılfenoxı)metıl)carbonıl-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((2-metoxicarbonılfenoxı)metil)carbonil-2,5-dimetıl-4-(4-fluorobencil)piperazına,

(*trans*)-1-((3- nıtrofenoxı)metil)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-acetıl-2-(amınocarbonıl)fenoxı)metil) carbonıl-2,5-dımetıl-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-nıtro-3-metılfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencıl)pıperazına;

(*trans*)-1-((5-nitro-2-metilfenoxi)metıl)carbonil-2,5-dimetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-amıno-3-nıtrofenoxı)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(*trans*)-1-((5- nıtro-2-amınofenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(*trans*)-1-((2-amınofenoxı)metıl)carbonıl-2, 5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((3- metoxıfenoxı)metıl)carbonil-2,5-dımetil-4-(4-fluorobencıl)pıperazina;

(*trans*)-1-((4-metoxı-2-acetılfenoxı)metıl)carbonil-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((5-metoxı-2-acetılfenoxı)metıl)carbonil-2,5-

dimetil-4-(4-fluorobencil) piperazina,

(*trans*)-1-((2-((2-hidroxietil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-((2-hidroxietoxi)carbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(2-hidroxietoxi)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(*trans*)-1-((2-acetil-4,5- dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((5-metoxi-2-(metoxicarbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(*N'*- metilureido)amino)metil)piperazina;

(*trans*)-1-((4- metil-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((3-cloro-5-metoxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metoxi-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-(hidroximetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2- (2-azidoetil)-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(ftalımıdo)fenoxı)metil)carbonil-2,5-dımetıl-4-(4- fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-(maleımıdo)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(*trans*)-1-((4-cloro-2-((4-(bencılcarbonıl) pıperazın-1-ıl)metil)fenoxi)metıl)-carbonıl-2,5-dimetil-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((4-((2,3, 4-trıfluorofenıl)aminocarbonıl)pıperazın-1-ıl)metıl)fenoxı)metıl) carbonil-2,5-dimetil-4-(4-fluorobencil)pıperazına;

(*trans*)-1-((4-cloro-2-((4-((2-fluorofenıl)amınocarbonıl)pıperazın-1-ıl)metil) fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((*N'*-(2,6-dıfluorofenil)ureido)fenoxi)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-(etenılcarbonılamıno)fenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-(cıclopropilcarbonılamıno)fenoxı)metıl)carbonıl-2,5- dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-(cıclopentılcarbonılamino)fenoxi)

metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((furan-2-il)carbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(fenilcarbonilamino)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-((*N'*-(3-metoxifenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(metoxicarbonilmetilcarbonil)-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(2-metoxicarboniletil)carbonil-*N'*-(metil)glicinamido)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-metilbencil)aminocarbonil- *N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-trifluorometil-4-fluorofenil)carbonil-*N'*-(metil)glicinamido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(4-metilbencil)aminocar-

bonil-*N'*-(metil)glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-clorofenil)carbonil-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(4-fluorobencil)aminocarbonil-*N'*-(metil)glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2-iodofenilcarbonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,3-difluorofenilcarbonil)glicinamido)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-((4-fenoxifenil)aminocarbonil)glicinamido)fenoxi)-metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diflurofenilcarbonil)glicinamido)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((2-iodofenilcarbonil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((etoxicarbonilmetilcarbonil)aminometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-

fluorobencil) piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(3-cloropropil)ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(2-fluoro-6-trifluorometilfenil)ureidometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((3-fluorofenil)carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-(2-(etoxicarbonil)etil)ureidometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(2*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((2,5-di(trifluorometil)fenil)carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, y

(*trans*)-1-((4-cloro-2-(*N'*-(2-(fenil)ciclopropil)ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

9. El compuesto de la reivindicación 7, en el que· R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8)alquilo y hidroxi(C1-C8) alquilo;

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R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (C3- C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8) alquilcarbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1- C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8) alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil) ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1- C8)alquil-

carbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

10. El compuesto de la reivindicación 9 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-((4-cloro-3-nitrofenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-2- (aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*S*,5*R*)-1-((4-bromo-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-1-((3-hidroxi-5-metilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2 *S*,5*R*)-1-((4-nitro-3-formilfenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(2R)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)car-bonil-2-(2-hidroxietil) piperazina;

(*trans*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5- dimetilpiperazina;

(*trans*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxietil)-5-metilpiperazina;

(2*R*,6*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2,6-dimetilpiperazina,

(*trans*)-1-((4-cloro-2- metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2-metil-4- (4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-3- (hidroximetil)fenoxi)me-til)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-hidroxietil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-aminofenoxi)metil) carbonil-2,5-

dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina,

(*trans*)-4-(4-fluorobencil)-1-((2-acetilamino-4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(*trans*)-1-((4-cloro-2-(propilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(metoximetilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-(metoxicarbonil)etil-carbonilamino)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-etoxicarbonil)etilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metilsulfonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(bromometilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(2*R*)-1-((4-cloro-2-(glicinamido) fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

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(*trans*)-1-((4-cloro-2-((*N'*-metilglicinamido)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(alaninamido)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((aminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminocarbonil)(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(*N'*-etiluredio)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(etilcarbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-amino-5-nitrofenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal diclorhidrato;

(*trans*)-1-((4-cloro-2-(((etil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((dietil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((ciclopropil)am-ino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-

fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(((dimetil)amino)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(((metil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((amino)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-metilpiperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-(etilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(metilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(metilsulfonil)(metil)aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*)-1-((4-cloro-2-((piperazin-1-il)metil) fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-2-((piperazın-1-ıl)metıl)fenoxı) metıl)carbonıl-2,5-dımetıl-4-(4-fluoroben-cıl)pıperazına;

(*trans*)-1-((4-cloro-2-((4-*t*-butoxıcarbonılpıperazın-1-ıl) metil)fenoxı)metıl)carbonıl-2,5-dımetil-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-(ımıdazol-1-ilmetil)fenoxı) metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(*trans*)-1-((4-cloro-2-(1-(ımıdazol-1-ıl)etıl)fenoxı)metıl)carbonıl- 2,5-dımetıl-4-(4-fluorobencıl)pıperazina;

(*trans*)-1-((4-cloro-2-(trıazol-1-ılmetılo)fenoxı)metil) carbonıl-2,5-dimetıl-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(tetrazol-1-ılmetıl)fenoxi)metil) carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((4-cloro-2-((morfolın-4-ıl)metıl)fenoxı)metıl)carbonıl-2,5-dımetıl-4-(4-fluorobencıl)pıperazına,

(2*R*)-1-((4-cloro-2-amınocarbonilfenoxi)metil)carbonil-2-metıl-4-(4-fluorobencıl) pıperazına;

1-((4-cloro-2-formılfenoxı)metıl)carbonıl-2- metıl-4-(4-fluorobencil)pıperazina,

(2*R*,5*S*)-1-((4- cloro-2-formılfenoxı)metil)carbonıl-2,5-dımetıl-4-(4-fluorobencıl) piperazina;

(2*R*)-1-((4-cloro-2-formilfenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metilaminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina,

(*trans*)-1-((4-cloro-2-((aminocarbonilmetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((2-aminoetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4- aminocarbonilo fenilo opcionalmente sustituido)aminocarbonil)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(hidroxiamidino)fenoxi)metil) carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-((*N'*-(triclorometilcarbonil) ureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(metoximetilcarbonil)glicinamido)fenoxi) metil)-carbonil-2,5-dimetil-4-(4-

fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-(*N'*-(etoxicarbonyiaminocarbonil) glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina.

11. El compuesto de la reivindicación 9, en el que R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y en la posición 2 por aminocarbonilo, ureido, o glicinamido, a saber, el compuesto seleccionado del grupo formado por los siguientes compuestos·

(2*R*,5*S*)-1-((4-cloro-2- (aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(glicinamido)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)- 1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(ureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*, 5*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina; y

(2*R*,5*S*)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

12 El compuesto de la reivindicación 9 en el que el compuesto más preferido es:

(2*R*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

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13 El compuesto de la reivindicación 3 en el que:

R^4 es

$-N(R^7)-$;

R^5 es

metileno,

R^6 es

$-C(O)-$; y

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo

14. El compuesto de la reivindicación 13 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)

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alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8) alquiltio(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8) alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8) alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, hidroxi(C1-C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1- C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azu-

fre)(C1-C8)alquilo,

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo,

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8) alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8)alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8) alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-

C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8) alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ((C1-C8) alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre) amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicar-

bonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi) carbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, (aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil) aminocarbonilo, di(C1-C8)alquilaminocar-bonil(C1-C8)alquilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil) glicinamido, (aminocarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbo-

nil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre) (C1-C8)alquilo.

15. El compuesto de la reivindicación 14 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1- C8) alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, cia-

no(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro,

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8) alcoxi, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido) (c1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(c1- C8)alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15

miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocar-

bonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)al-quil)aminocarbonilo, (hidroxi(C1-C8)al-quil)amino-carbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcional-mente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sus-tituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcio-nalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)al-quilo, (halo(C1- C8)alquil)((C1-C8)alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8) al-quil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8) alquilcarbonil)((C1-C8)al-quil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo op-cionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-

C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(c1-C8) alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

16. El compuesto de la reivindicación 15 en el que·

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8) alquilo y hidroxi(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-

C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (3C-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8) alquilcarbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8)alquil-sulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8) alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil) ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1- C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

17 El compuesto de la reivindicación 16 en el

que R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido

18. El compuesto de la reivindicación 17 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-((4-clorofenilamino)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(aminocarbonil)fenilamino)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina; y

1-((4-clorofenilamino)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina.

19. El compuesto de la reivindicación 3 en el que:

R^4 es

$-C(R^8)_2-$;

R^5 es

metileno,

R^6 es

-C(O)-, y

cada R^8

se selecciona en forma independiente entre el grupo formado por hidrógeno, (C1- C8) alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8) alquilcarbonilamino,

(C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre) carbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1- C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, y di(C1-C8)alquilamino(C1-C8)alquilo.

20. El compuesto de la reivindicación 19 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidr-

oxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8) alquiltio(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8) alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil) ureido(C1-C8)alquilo, hidroxi(C1- C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1- C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo;

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8) alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquil-

carbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros

que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxigeno y azufre)amino(C1-C8) alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hi-

droxi(C1-C8) alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil) aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, di(C1-C8) alquilaminocarbonil(C1-C8) alquilo, hidroxiamidino, ureido, mono(C1-C8) alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)· alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente

sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (3-15membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

21. El compuesto de la reivindicación 20 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8) alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, (fe-

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nilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (3- 15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10)cicloalquilamino(C1-C8) alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo

formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil) amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino (C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo; (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)al-

quil)aminocarbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil) ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbo-nil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonil)

((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno,oxígeno y azufre)(C1-C8)alquilo.

22. El compuesto de la reivindicación 21 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8) alquilo y hidroxi(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8)alquilcarbonilamino,

halo(C1-C8)alquilcarbonilamino, (C1-C8) alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8) alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1- C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

23. El compuesto de la reivindicación 22 en el que:

R^2 es

4- fluoro,

R^3 es

fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido; y

un R^8 es

hidrógeno y el otro R^8 es seleccionado del grupo formado por amino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre) carbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, y amino(C1-C8)alquilo.

24. El compuesto de la reivindicación 23 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-(2-(4-clorofenil)-3- (metilsulfonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(acetilamino) propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(metilsulfonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(acetilamino)etil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(amino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(ureido)etil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-amino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*t*-butoxicarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((etoxicarbonilmetilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluo-

robencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'-iso*-propil-ureido)etil)carbonil-2,5-dimetil-4-(4-fluoro-bencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-(2-cloro-etil)ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2-nitrofenil)carbonil-amino)etil)carbonil-2,5-dimetil-4-(4-fluoro-bencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((4-metoxifenilmetil)car-bonilamino)etil)carbonil-2,5-dimetil-4-(4-fluo-robencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2,4-dinitrofenil)sulfo-nilamino)etil)carbonil-2,5- dimetil-4-(4-fluoroben-cil)piperazina,

(*trans*)-1-(2-(4-clorofenil)-2-(ciclopropilcarbonilami-no)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)pi-perazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2-ciclopropiletil)car-bonilamino)etil)carbonil-2,5-dimetil-4-(4- fluoro-bencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-((2-metilpropil)carbonil-amino)propil)carbonil-2,5-dimetil-4-(4- fluoroben-cil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(cicloppentilcarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(*t*-butil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(etil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(3-choropropil) ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-(2-(4-clorofenil)-3-((morfolin-4-il)carbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

25. El compuesto de la reivindicación 1 en el que:

R^3 es

un sistema de anillo heterocíclico sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8) alquilo, (C1-C8)alquilsulfonilo, (fenilo o naftilo opcionalmente sustituido) sulfonilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, halo(C1-C8) alcoxi, (C2-C8)alquenilo,

(C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido) (C1-C8)alquilamino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8) alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente susti-

tuido)(C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, guanidino, ureido, mono(C1- C8) alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, y glicinamido

26 El compuesto de la reivindicación 25 en el que

R^4 es

-O-, - $N(R^7)$- o -$C(R^8)$-;

R^5 es

una cadena (C1-C8) alquileno;

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) al-

quilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10)cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8)alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonil)((C1-C8)alquil)amino, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consis-

te de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1- C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, carboxi(C1-C8) alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo,y di(C1-C8) alquilaminocarbonil(C1-C8)alquilo.

27. El compuesto de la reivindicación 26 en el que:

R^4 es -O-;

R^5 es metileno; y

R^6 es -C(O)-

28. El compuesto de la reivindicación 26 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8) alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8)alquilo, hidroxi(C1-C8) alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, hidroxi(C1- C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-

C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo; y

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo.

29. El compuesto de la reivindicación 28 R^3 seleccionado del grupo formado por azepinilo, acridinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, benzopiranilo, benzopiranonilo, benzofuranilo, benzofuranonilo, benzotienilo, carbazolilo, cinnolinilo, decahidroisoquinolilo, dioxolanilo, furilo, isotiazolilo, quinuclidinilo, imidazolilo, imidazolinilo, imidazolidinilo, isotiazolidinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, indanilo, indolizinilo, isoxazolilo, isoxazolidinilo, morfolinilo, naftiridinilo, oxadiazolilo, octahidroindolilo, octahidroisoindolilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxoazepinilo, oxazolilo, oxazolidinilo, piperazinilo, 4- piperidonilo, fenazinilo, fenotiazinilo, fenoxazinilo, ftalazinilo, pteridinilo, purinilo, pirrolilo, pirazolilo, pirazolidinilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, quinazolinilo, quinoxalinilo, quinolinilo, quinuclidinilo, isoquinolinilo, tiazolilo, tiazolidinilo, tiadiazoli-

lo, triazolilo, tetrazolilo, tetrahidrofurilo, tetrahidropiranilo, tienilo, tiamorfolinilo, tiamorfolinilo sulfóxido, y tiamorfolinilsulfona.

30. El compuesto de la reivindicación 29 en el que R^3 es benzopiranilo, benzopiranonilo, benzfuranilo, benzofuranonilo, quinolinilo, indolilo, indolinilo, oxazolilo, imidazolilo, o benzotienilo.

31. El compuesto de la reivindicación 30, a saber: (*trans*)-1-((benzo[b]piran-2-on-7- iloxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

32. Los compuestos

(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpiperazin-1-il]-3-oXopropenil]- fenil)-urea,

N-(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpiperazin-1-il]-3- oxopropenil] fenil)-metansulfonamida,

(5-Cloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobencil)-2,5-dimetilpiperazin-1-il]-3-oxopropenil]-fenil)-urea,

N-(5-Cloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobencil)-2, 5-dimetilpiperazin-1-il]-3-oxopropenil]-fenil)-metansulfonamida,

metiléster de ácido (5-Cloro-2- {(E)-3-[4-(4-fluorobencil)-2-metil-piperazin-1-il]-3-oxo-propenil}- fenil)-acético,

ácido 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metilpiperazin-1-il]-3-oxo-propenil}- benzoico,

(5-cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxo-propenil}-4-metoxi-fenil)-urea,

(5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxopropenil}-4-trifluorometoxi-fenil)-urea,

metiléster de ácido 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il}-3-oXo-propenil}-4-metoxi-benzoico

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-propiónico,

ácido (5-Cloro-2-{2-[4-(3,4-difluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[4-(4-cloro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Cloro-2-{2-[4- (4-cloro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[4-(3, 4-difluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acé-tico,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxv}-fenil)-acrílico,

N-[(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acetil]-metansulfonamida,

N-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-benzoil)-metansulfonamida,

N- [(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acetil]-C,C,C-trifluoro-metansulfonamida,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-oxo- acético,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)- acético,

ácido 2-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-ill-2-oxo-etoxi}-fenoxi)-2-metil- propiónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-di-

metil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)-difluoro-acético

(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfonamida

N-{5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]fenil-trifluorometansulfonamida,

5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-bencensulfonamida.

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5- Bromo -2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-etansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfónico,

monoetiléster de ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R, 5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil) fosfónico,

ácido 5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfonamídico

metiléster de ácido 5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético;

metiléster de ácido 5-bromo-2-[2-[(2*R*)-4-[(4- fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluoro-

fenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metilbenzoico,

metiléster de ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico;

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-(trifluorometil)benzoico;

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]benzoico;

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*)-4-[(5-cloro-2-tienil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencensulfónico;

ácido 5-cloro-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencensulfónico;

ácido 5-cloro-4-(dimetilamino)-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-

dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético

ácido 5-bromo-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencen acético;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metil- benzoico

ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico.

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-(trifluorometil) benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxi-benzoico;

ácido 5-cloro-4-etoxi-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 4-amino-5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)me-

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til]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 4-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-5-metil benzoico

en la producción de un medicamento para el tratamiento y la prevención de la endometrosis en seres humanos

33. Una composición farmacéutica útil para el tratamiento de la endometrosis en un humano de sexo femenino que necesita dicho tratamiento, que comprende una cantidad eficaz en términos terapéuticos de un compuesto de acuerdo con la reivindicación 1.

el acceso al transportador 32. El proveedor de servicios es capacitado para colocar los elementos a ser transferidos hacia un cliente en un área interior del transportador cuando el transportador está posicionado en la estación de proveedor de servicios. En una forma preferida del invento los elementos a ser transferidos comúnmente incluyen elementos médicos, folletos de instrucciones, dinero y monedas, comprobantes de tarjetas de crédito, recibos y prescripciones y otros documentos y cosas que pudieran razonablemente esperarse ser intercambiadas en una transacción relacionada con la compra de elementos médicos. En una forma preferida del invento el transportador 32 preferiblemente tiene un diámetro de aproximadamente 20,32 a 25,4 cm, y una altura suficientemente grande para permitir el transporte de los tipos y cantidades deseados de elementos. Cuando el invento es utilizado en otros tipos de ambientes de transacciones, otros elementos pueden ser transferidos en el transportador y otros tamaños y configuraciones de transportador, tubo y terminales puede ser utilizados.

La apertura de transferencia 48 de la realización mostrada preferiblemente incluye una puerta 50. Como se muestra en la figura 4, la puerta 50 es preferiblemente una puerta del tipo

Fig. 1

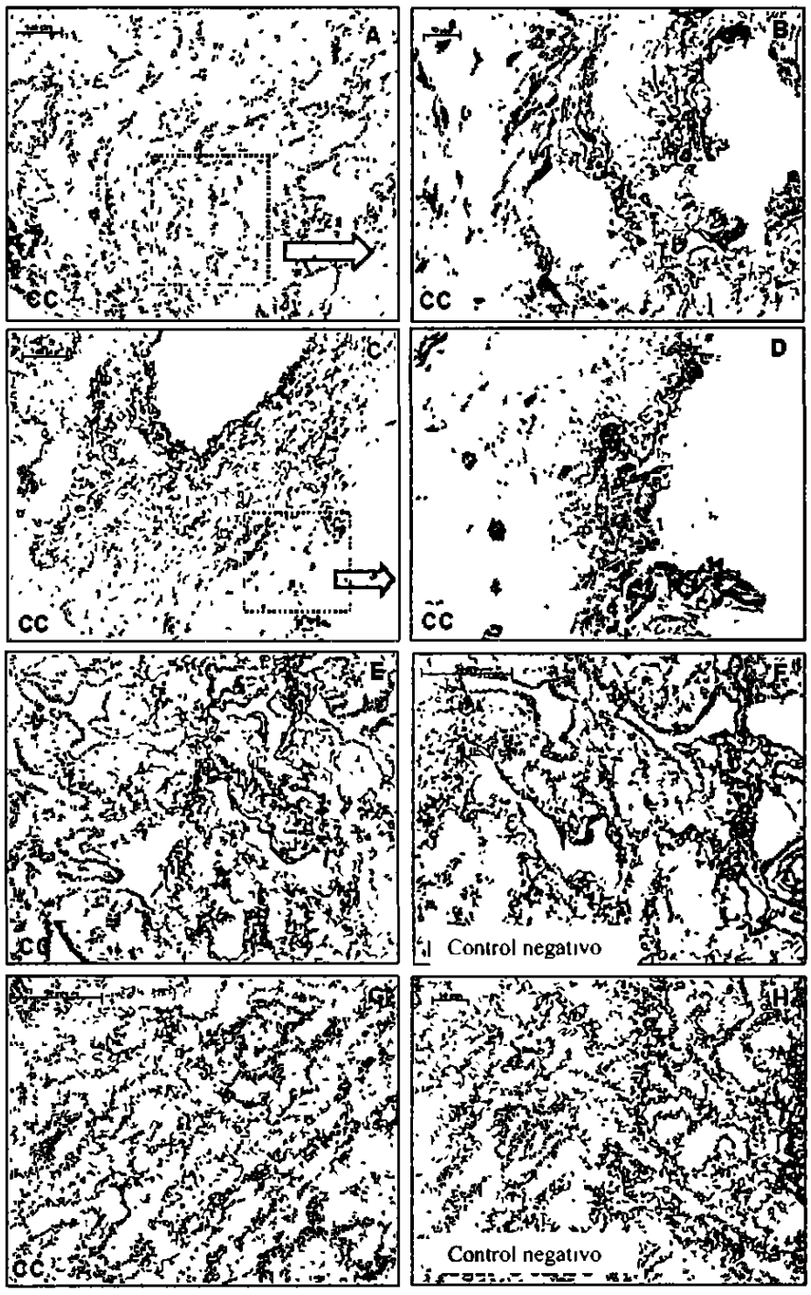
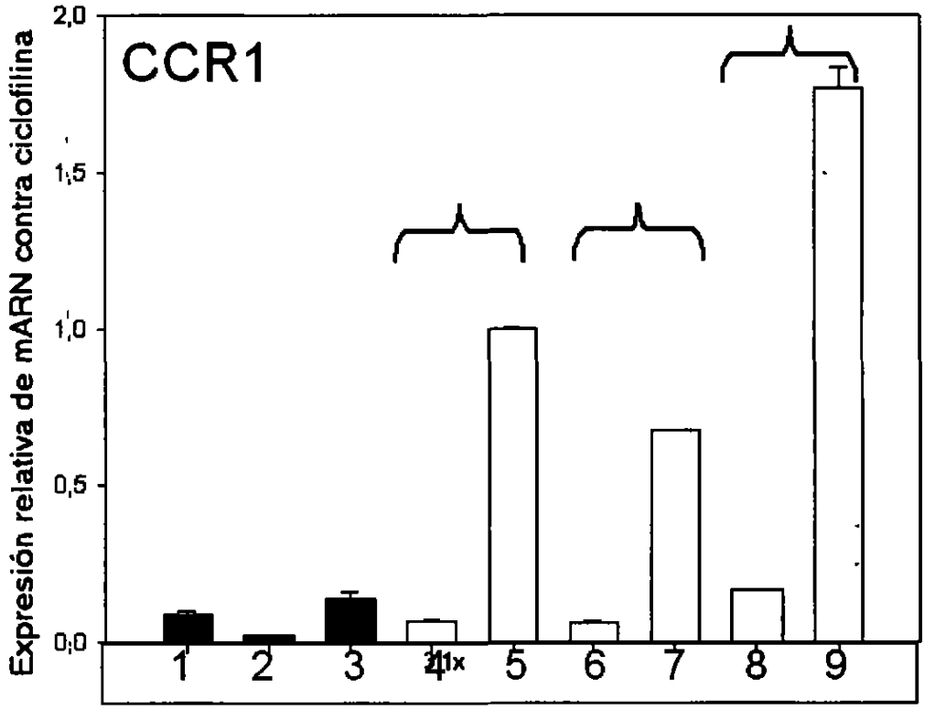

A
CC
B
CC
C
CC
D
CC
E
CC
F
Control negativo
G
CC
H
Control negativo

Fig. 2


CCR1
Expresión relativa de mARN contra ciclofilina
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1,0
0,5
0,0
1
2
3
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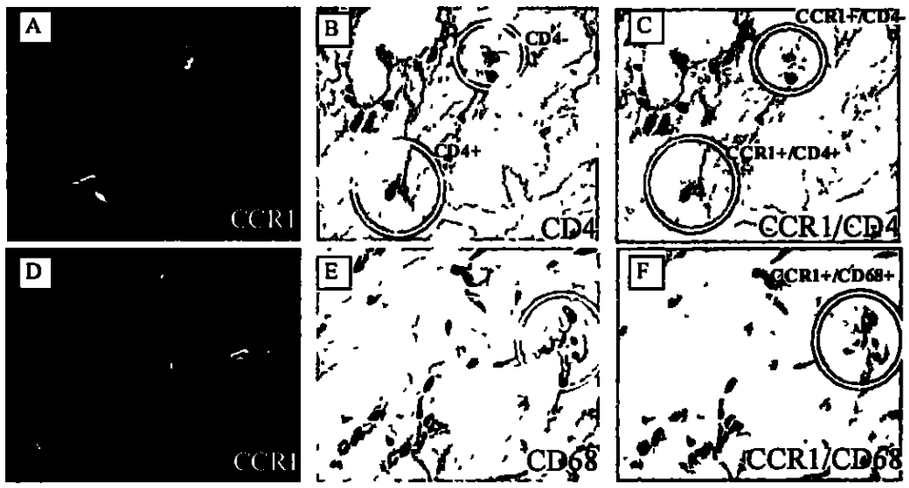
5
6
7
8
9

Fig. 3


A
CCR1
B
CD4-
CD4+
CD4
C
CCR1+/CD4-
CCR1+/CD4+
CCR1/CD4
D
CCR1
E
CD68
F
CCR1+/CD68+
CCR1/CD68

833

Fig. 4

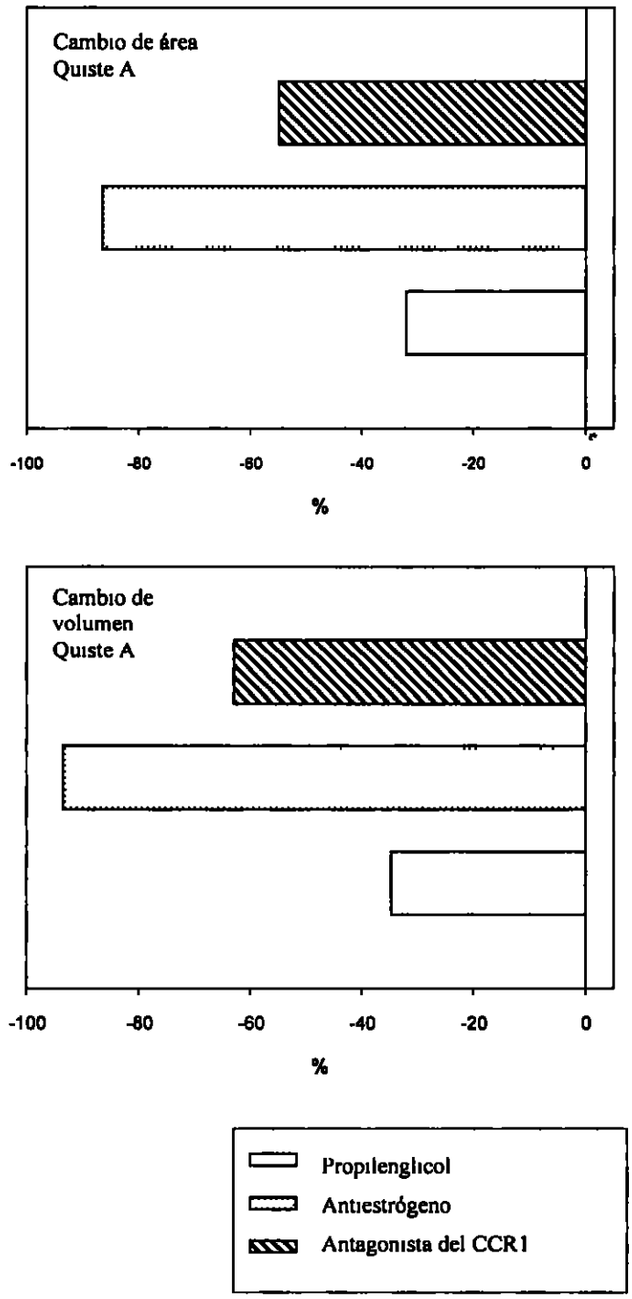

Cambio de área
Quiste A
-100
-80
-60
-40
-20
0
%
Cambio de
volumen
Quiste A
-100
-80
-60
-40
-20
0
%
Propilenglicol
Antiestrógeno
Antagonista del CCR1

Fig. 5a

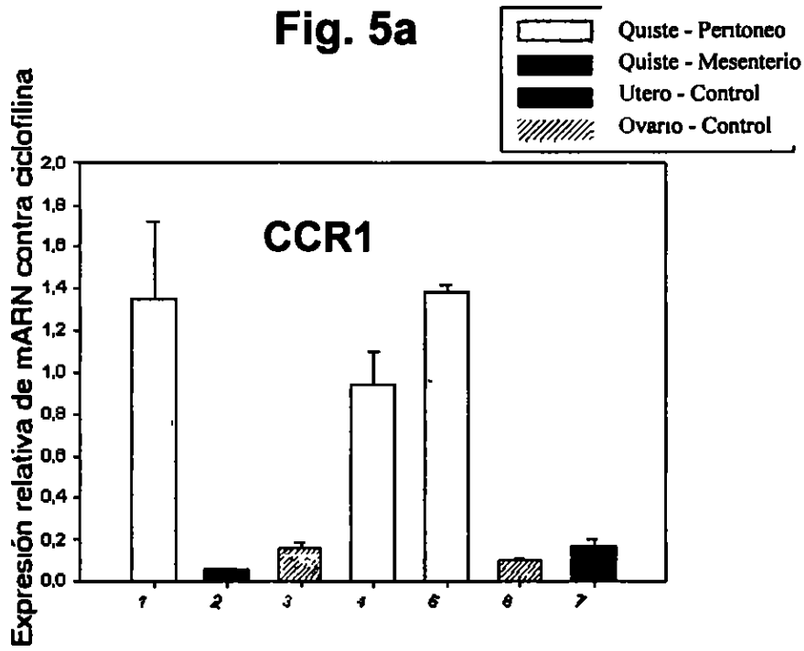

Quiste - Peritoneo
Quiste - Mesenterio
Utero - Control
Ovario - Control
CCR1
Expresión relativa de mARN contra ciclofilina
2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
1
2
3
4
5
6
7

Fig. 5b

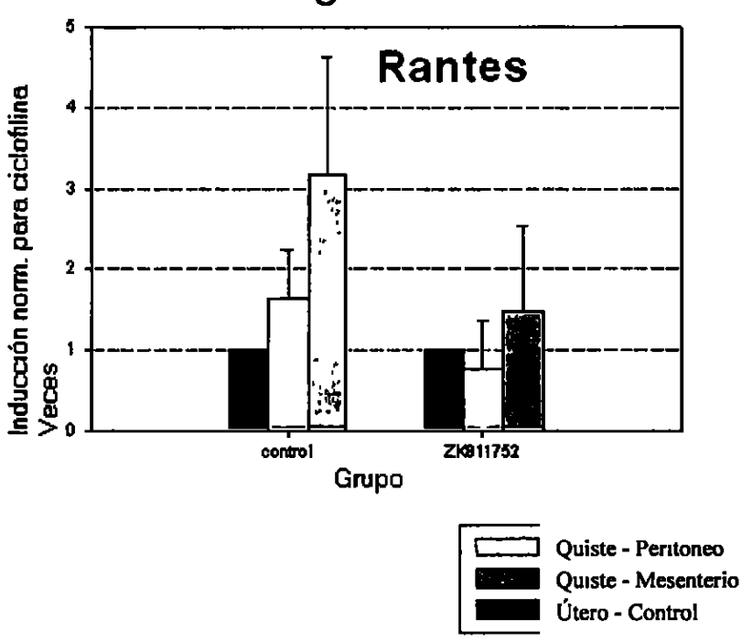
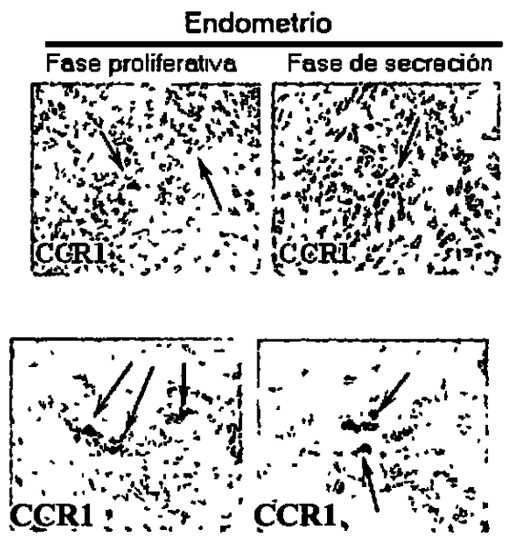

Rantes
Inducción norm. para ciclofilina
Veces
5
4
3
2
1
0
control
ZK811752
Grupo
Quiste - Peritoneo
Quiste - Mesenterio
Útero - Control

Fig. 6a

Número de células CCR1-teñidas durante el ciclo menstrual

	PP	SP	M
Endometrio	10	15	22
Injertos	66	101	43

Fig. 6b



Injertos Endometriósicos

PP = Fase Proliferativa
SP = Fase de Secreción
SP = Fase de Secreción

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

836

Remitente EL ORGANISMO DE EXAMEN PRELIMINAR INTERNACIONAL

A

SCHERING AKTIENGESELLSCHAFT
Mullerstrasse 178
13342 Berlin
Alemania

PCT

NOTIFICACIÓN DE ENVÍO DEL INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

(regla PCT Nº 71 1)

Fecha de envio (*dia/mes/año*)	*11 05 2006*
Referencia del Solicitante o Agente *531894WO*	**NOTIFICACIÓN IMPORTANTE**

Referencia Internacional	Fecha de Presentación Internacional (*dia/mes/año*)	Fecha de Prioridad (*dia/mes/año*)
PCT/EP 2005/002036	*23 02 2005*	*24 02 2004*

Solicitante SCHERING AKTIENGESELLSCHAFT et al

1 Se notifica al solicitante que el organismo encargado del Examen Preliminar Internacional envia mediante la presente el informe de Examen Preliminar Internacional elaborado para esta Solicitud Internacional, en casos dados, con los anexos correspondientes

2 Una copia del informe – en casos dados, con los anexos correspondientes – es enviada a la Oficina Internacional para su derivación a todos los organismos seleccionados

3 A peticion de un organismo seleccionado, la Oficina Internacional traducirá el informe (pero no sus anexos) al ingles y lo enviará a tal organismo

4 **RECORDATORIO**

Para el ingreso en la fase nacional, el solicitante debe proceder, dentro de los 30 meses de la fecha de prioridad (o más tarde en otros organismos), a llevar a cabo ciertos trámites (presentación de traducciones y pago de tasas nacionales) (articulo 39 (1)) (ver también la información brindada por la Oficina Internacional por medio del formulario PCT/IB/301)

Cuando se debe enviar a un organismo seleccionado una traducción de la solicitación internacional, esta traduccion debe contener también las traducciones de todos los anexos del informe del Examen Preliminar Internacional Es responsabilidad del solicitante elaborar tales traducciones y enviarlas directamente al organismo correspondiente seleccionado

Otros detalles de los plazos y requisitos normativos de los organismos seleccionados se pueden tomar del Manual PCT para solicitantes

El solicitante es advertido acerca del articulo 33 (5) en el cual se aclara que los criterios de novedad, actividad inventiva y aplicabilidad industrial descriptos en el artículo 33 (2) a (4) solo tiene significado para el Examen Preliminar Internacional, y que "cada estado adherido ( ) puede disponer atributos adicionales o modificatorios en tal estado para la determinacion de la patentabilidad de la invención reivindicada " (ver también articulo 27 (5)) Tales atributos adicionales se pueden referir, por ejemplo, a excepciones de patentabilidad, a requisitos para la revelacion de la invencion, así como a claridad y apoyo de los reivindicaciones

Nombre y Direccion Postal del Organismo encargado del Examen Preliminar Internacional Europaisches Patentamt D-80296 Munich Tel +49 89 2399-0, Tx 523656 epmu d Fax +49 89 2399-4465	Funcionario Apoderado *Ullrich, J* Tel +49 89 2399-7530

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD

(Capítulo II del Tratado de Cooperación Internacional en Materia de Patentes)

(Artículo PCT 36 y regla PCT 70)

Referencia del Solicitante o Agente *53189AWO*	**PROCEDER** Ver formulario PCT/IPEA/416)	
Referencia Internacional *PCT/EP 2005/002036*	Fecha de Presentación Internacional (*día/mes/año*) *23 02 2005*	Fecha de Prioridad (*día/mes/año*) *24 02 2004*
Clasificación Internacional de Patente (CIP) o Clasificación Nacional y CIP *INV A61K31/495 A61K31/00*		
Solicitante *SCHERING AKTIENGESELLSCHAFT et al*		

1 Este informe se trata del Examen Preliminar Internacional, confeccionado por el organismo encargado del Examen Preliminar Internacional según el artículo 35 y enviado al solicitante según el artículo 36

2 Este INFORME comprende, en total, 5 hojas, incluida esta carátula

3 Además, este informe posee ANEXOS, los mismos comprenden

a ☒ (*remitidos al solicitante y a la Oficina Internacional*) en total hojas, aquí se trata de

☒ hojas con las descripciones, reivindicaciones, y/o ilustraciones que fueron modificadas y en las cuales se basa este informe y/u hojas con correcciones que aprobó el organismo (ver regla 70 16 y sector 607 de los reglamentos administrativos de PCT)

o ☐ hojas que reemplazan hojas anteriores pero que, según opinión del organismo, contienen una modificación por los motivos indicados en el campo Nº 1, punto 4, superando el contenido revelado en la Solicitud Internacional en la versión presentada originalmente

b ☐ (*remitidos solo a la Oficina Internacional*) en total (rogamos indicar tipo y cantidad del (los) soporte(s) electrónico(s) que contiene(n), solo en forma legible por computadora, el (los) protocolo de secuencias y/o las tablas correspondientes tal como está indicado en el campo suplementario refendo al protocolo de secuencias (ver sector 802 de las normas administrativas)

4 Este informe contiene indicaciones acerca de los siguientes puntos

☒	Campo Nº I	Fundamento del informe
☐	Campo Nº II	Prioridad
☐	Campo Nº III	No realización de ningun dictamen sobre novedad, actividad inventiva y aplicabilidad industrial
☐	Campo Nº IV	Falta de uniformidad de la invención
☒	Campo Nº V	Resolución fundada segun regla PCT 43*bis* 1(a)(i) con respecto a la novedad, la actividad inventiva y la aplicabilidad industrial, documentos y aclaraciones destinadas a apoyar esta resolución
☐	Campo Nº VI	Documentos especificos expuestos
☐	Campo Nº VII	Carencias especificas de la solicitud internacional
☐	Campo Nº VIII	Observaciones específicas a la solicitud internacional

Fecha de presentación de la solicitud *23 12 2005*	Fecha de confección de este informe *11 05 2006*
Nombre y Direccion Postal del organismo encargado del Examen Internacional Oficina de Patentes Europea D-80298 Munich Tel ++49 89 2399-0, Tx 523656 epmu d Fax +49 89 2399-4465	Funcionario Apoderado *Johnson, C* Tel *+49 89 2399-8287*

Formulario PCT/IPEA/409 (caratula)(abril 2005)

838

Campo Nº I Fundamento del Informe

1 Con respecto al **idioma**, el informe está basado sobre la solicitud internacional en el idioma en que fue presentada, en tanto en este punto no se indique otra cosa

☒ la solicitud internacional en el idioma en que fue presentada

☐ El informe está basado sobre una traducción del idioma original al siguiente idioma, el que se trata del idioma de la traducción suministrada a los siguientes efectos:
- ☐ búsqueda internacional (según reglas 12.3 y 23 1 b))
- ☐ publicación de la solicitud internacional (según regla 12 4)
- ☐ examen preliminar internacional (según regla 55 2 y 55 3)

2 Con respecto a los **elementos*** de la Solicitud Internacional, el informe se basa en *(las hojas de reemplazo que fueron presentadas al organismo como requisito según el artículo 14 son válidas como "presentadas originalmente" en el marco de este informe y no se adjuntan)*

Descripción, páginas

1, 2, 4 – 10, 12 - 230	en la versión presentada originalmente
3, 3a, 11	presentadas con la solicitud

Reivindicaciones, Nº

1 – 33	presentadas con la solicitud

Ilustraciones, hojas

1 – 6	en la versión presentada originalmente

☐ un listado de secuencias y/o eventual(es) tabla(s) relacionada(s) – con respecto al protocolo de secuencias, ver campo adicional

3 ☐ Como consecuencia de las modificaciones caducaron los siguientes documentos

- ☐ Descripción páginas
- ☐ Reivindicaciones Nº 11 – 13
- ☐ Ilustraciones hoja/figura
- ☐ Listado de secuencias *(especificar)*.
- ☐ Eventuale(s) tabla(s) perteneciente(s) al listado de secuencias *(especificar)*

4 ☐ Este informe fue elaborado sin tomar en consideración (algunas de) las modificaciones, dado que las mismas, según opinión del organismo y por los motivos expresados, exceden el contenido revelado en el texto presentado originalmente (regla 70 2(c)), tal como se indica en el campo suplementario

- ☐ Descripción páginas
- ☐ Reivindicaciones Nº
- ☐ Ilustraciones hojas/figuras
- ☐ Listado de secuencias *(especificar)*
- ☐ Eventuale(s) tabla(s) perteneciente(s) al listado de secuencias *(especificar)*

* *Cuando corresponde el punto 4, algunas o todas estas hojas pueden estar provistas de la observación "reemplazada"*

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Campo Nº V **Resolución fundada según el artículo 35(2) con respecto a la novedad, la actividad inventiva y la aplicabilidad industrial; documentos y declaraciones destinadas a apoyar esta resolución**

1 Resolucion

Novedad (N)	SI	Reivindicaciones	1 – 33
	No	Reivindicaciones	
Actividad inventiva (IS)	SI	Reivindicaciones	1 – 33
	No	Reivindicaciones	
Aplicabilidad industrial (IA)	SI	Reivindicaciones	1 – 33
	No	Reivindicaciones	

2 Documentos y aclaraciones (regla 70 7)

ver hoja adjunta

840

V Resolución fundada

Se hace referencia a los siguientes documentos.
D1 EP-A-1 254 899
D2 WO2004/002960

Novedad

Las reivindicaciones conciernen al uso de compuestos que responden a la formula (Ia) en la producción de un medicamento para el tratamiento y la prevención de la endometrosis
D1 revela como agentes antiinflamatorios compuestos que corresponden a la presente fórmula (Ia) pero no menciona su uso en el tratamiento de la endometrosis Los compuestos de D2 difieren de los presentes compuestos utilizados, entre otras cosas, en que el anillo piperazina está adjuntado al anillo quinolina
Las reivindicaciones 1 – 33 cumplen los requisitos del artículo PCT 33(2)

Actividad inventiva

D1 revela el uso de compuestos que caen en el ámbito de la presente fórmula (Ia) como inhibidores de la quimioquinas, MIP-1α y RANTES, en el tratamiento de astomos inflamatorios en humanos
D2 declara que "la producción anormal de quimioquinas tales como RANTES y MIP-1a ha sido involucrada en un amplio rango de enfermedades inflamatorias humanas agudas y crónicas, incluyendo artritis reumatoidea, esclerosis múltiple, enfermedad inflamatoria del intestino, endometrosis, enfermedades respiratorias tales como asma, y trastornos alérgicos"
El problema técnico parece ser la disponibilidad de un tratamiento efectivo de la endometrosis
Aunque D2 enseña que la quimioquina RANTES (conocida por ligar con receptores de CCR1, CCR3 y CCR5) puede estar involucrada en enfermedades inflamatorias, incluyendo endometrosis, el experto no está al tanto del hecho de que antagonistas selectivos de receptores de CCR1 pueden ser particularmente útiles en el tratamiento de la endometrosis En la figura 2 de la solicitud se muestra que la CCR1 mRNA es muy significativamente sobreegulada en lesiones endométricas en comparación con tejidos endométricos normales Este conocimiento parece no haber estado disponible para el experto a la fecha de prioridad de la solicitud En consecuencia, parece no haber sido obvio para el experto utilizar específicamente un antagonista selectivo de CCR1 antes que otros competidores de RANTES tales como antagonistas de CCR5, con la esperanza de uqe fuera particularmene efectivo contra la endometrosis El presente objeto reivindicado, en tanto no posea el efecto alegado, puede por ello ser considerado inventivo
Las reivindicaciones 1 – 33 cumplen los requisitos del artículo PCT 33(3)

Aplicabilidad industrial

Las reivindicaciones 1 – 33 cumplen los requisitos del artículo PCT 33(4)

(Hoechst) describe derivados de piperazina que son útiles como agentes cardiotónicos. La solicitud publicada de patente europea 0 190 685 (G. D. Searle) describe derivados de piperazina que bloquean la vía metabólica de la 5-lipooxigenasa de la cascada del ácido araquidónico, y por lo tanto son útiles en el tratamiento de reacciones alérgicas y de hipersensibilidad e inflamación. La solicitud publicada de patente PCT, WO 96/34864 (Schering Plough) revela derivados de piperazina útiles como antagonistas de neuroquinina.

La solicitud publicada de patente europea 1 254 899 (Schering AG) revela los derivados de piperazina comprendidos en la presente solicitud para el tratamiento de un trastorno inflamatorio.

La solicitud de patente PCT WO 02/36581 (Schering AG) revela también derivados de piperazina comprendidos en la presente solicitud para el diagnóstico de la enfermedad de Alzheimer.

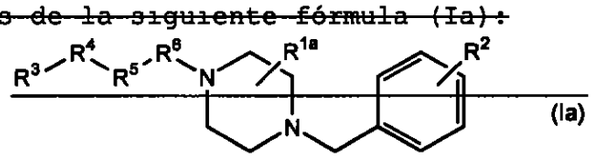
Todas las referencias anteriores se incorporan aquí en su totalidad como referencia.

Ninguna de las referencias anteriores describe los derivados de piperazina comprendidos en la presente solicitud para el tratamiento de la endometrosis en mujeres, donde dichos derivados de piperazina son antagonistas de Receptor 1 de Quimioquina Humana "C-C" (CCR1).

~~RESUMEN DE LA INVENCIÓN~~

~~Esta invención se relaciona con el uso de un compuesto de la siguiente fórmula (Ia) o su sal aceptable para uso farmacéutico para el tratamiento y prevención de la endometrosis en seres humanos en donde el tratamiento comprende administrar a un humano de sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de dicho compuesto.~~

~~De acuerdo con esto, en un aspecto, esta invención provee compuestos de la siguiente fórmula (Ia):~~



(Ia)

~~en donde:~~

~~R^{1a} es~~

~~uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por oxo, halo, alquilo, cicloalquilo, cicloalquilalquilo, cicloalquilaminoalquilo, (cicloalquilalquil)aminoalquilo, haloalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, formilo, formilalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, mercaptoalquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, (alcoxi)aralquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltioalquilo,~~

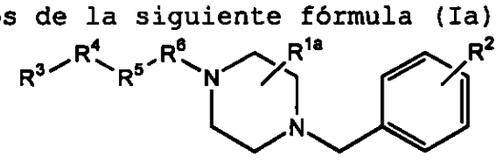
La WO 2004002960 A describe derivados de piperazina en los cuales la piperazina está adjuntada a un anillo de quinolina. Tales compuestos están descriptos a modo de antagonistas selectivos para la quimioquina humana "receptor C-C 5" (CCR 5). Según la WO 20054002960a, una de las condiciones de trastorno en las cuales está implicados los antagonistas de CCR5 es la endometrosis.

Los compuestos de la WO 2004002960 A poseen una estructura diferente y son activos sobre un receptor distinto.

RESUMEN DE LA INVENCIÓN

Esta invención se relaciona con el uso de un compuesto de la siguiente fórmula (Ia) o su sal aceptable para uso farmacéutico para el tratamiento y prevención de la endometrosis en seres humanos en donde el tratamiento comprende administrar a un humano de sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de dicho compuesto.

De acuerdo con esto, en un aspecto, esta invención provee compuestos de la siguiente fórmula (Ia):



(Ia)

en donde:

R^{1a} es

uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por oxo, halo, alquilo, cicloalquilo, cicloalquilalquilo, cicloalquilaminoalquilo, (cicloalquilalquil)aminoalquilo, haloalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, formilo, formilalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, mercaptoalquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, (alcoxi)aralquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltioalquilo,

(C=ONH-(C1-C8)alquilo, (C1-C8)alquil-SO2-NH-(C1-C8)alquilo, (C2-C9)heteroaril-(C1-C8)alquilo, H2N-(C=O)-,H2N- (C=O)- (CI-C8) alquil-;

cada R4 se selecciona en forma independiente entre el grupo formado por: H-, HO-, halo-, NC-, HO-(C=O-, H2N-, (C1-C8)alquil-NH-, [(C1-C8)alquil]2N-, (C1-C8)alquil-opcionalmente sustituido con 1-3 átomos de flúor,(C1-C8) alquil-O- en donde el grupo alquilo es opcionalmente sustituido con 1-3 átomos de flúor, HO-(C1-C8)alquil-, (C1-C8)alquil-O-(C1-C8)alquil-, H2N-(C1-C8)alquil-, (C1-C8)alquilo NH-(C1-C8)alquil-, [(C1-C8)alquil]2N-(C1-C8)alquil-, (C1-C8)alquil-(C=O)-, (C1-C8)alquil-(C=O)-(CC8) alquil-, (C6-C10)aril-, (C2-Cg) heteroaril-, (C6-C10) ariloxi, H2N-(C=O), H2N-(C=O)-(CC8) alquilo, (C1-C8)alquil-NH-(C=O)-, (C1-C8)alquil-NH-(C=O)-(C1-C8)alquil-, [(C1-C8)alquil]2N (C=O)-, [(C1-C8)alquil]2-N-(C=O)-(C1-C8)alquil-, (C3-C8)cicloalquil-, (C1-C8)alquil-SO2-, NC-(C C8)alquil-, (C1-C8) alquil-(C=O)-NH-, H2N-(C=O)-NH-, H2N-(C=O)-NH-(C1-C8) alquil-;

R5 es (C1-C8) alquil-.

para el tratamiento y prevención de la endometrosis.

Algunas realizaciones particularmente favorables de la presente invención son los siguientes compuestos según se informan en ~~WO01/72728~~ WO02/102787:

i1 (cont.)

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-me-til-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

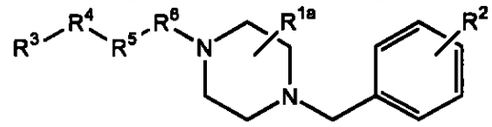
ácido (5- Bromo -2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- etansulfónico,

|La solicitud de patente WO2004/055031 en su totalidad se incorpora por referencia a la presente solicitud. Algunas formas de realización ventajosas de acuerdo con la presente invención son los compuestos de la fórmula I- WO2004/055031

REIVINDICACIONES

1. Uso de un compuesto de la siguiente fórmula (Ia):



(Ia)

en la producción de un medicamento para el tratamiento y la prevención de la endometrosis en seres humanos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por oxo, halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, ((C3-C10)cicloalquil(C1-C8)alquil) amino(C1-C8)alquilo, halo(C1-C8)alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2- C8)alquenilo, formilo, formil(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, mercapto(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-

C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8) alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8) alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, azido(C1-C8)alquilo, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8) alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo,

(fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8) alquilo, (C1-C8)alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a

15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto, mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsufonilo, (C1- C8)alquiltio(C1-C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8) alquilsulfonil(C1-C8)alquilo, (C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi, halo(C1-C8) alcoxi, (C3-C10)cicloalquilo, (C3-C10)cicloalquil(C1-C8)alquilo, (hidroxi)(C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino, (C3-C10) cicloalquilamino(C1-C8)alquilo, ((C3-C10)cicloalquil(C1-C8)alquil)amino, ((C3-C10)cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, ciano(C1-C8)alquilo, (C2-C8) alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo

opcionalmente sustituido)(C2-C8)alquenilo, hidroxi(C1-C8)alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8) alquinilo, (C1-C8)alcoxi(C1-C8)alquilo, ((C1-C8)al-coxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1- C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8) alquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino, ((C1-C8) alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8)al-

coxicarbonilamino(C1-C8) alquilo, ((C1-C8)alcoxi-carbonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxı, (C1-C8)alcox-icarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxicarbonilo, (C1-C8)alquılcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquılo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenılo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustıtuido)(C1-C8)alquılcarbonil(C1-C8)alquilo, carboxı(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquılo, (fenılo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbony((C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquılcarboniloxi(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquılamınocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquılamı-nocarbonilo, amınocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonıl(C1-C8)alquilo, di(C1-C8)al-quılaminocarbonil(C1- C8)alquilo, mono(fenilo o naftılo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenılo o naftilo opcionalmente sustıtuıdo)(C7-C8) alquılaminocarbonil(C1-

C8)alquilo, amidino, guanidino, ureido, mono(C1-C8) alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (3-15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^3 es

un sistema de anillo carbocíclico de 3 a 15 miembros sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto, mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsufonilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, (C1-C8)alquiltio(C1- C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8) alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo

opcionalmente sustituido)(C1-C8) alcoxi, halo(C1-C8)alcoxi, amino(C1-C8)alcoxi, (C3-C10)cicloalquilo, (C3- C10)cicloalquil(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino, (C3-C10)cicloalquilamino(C1-C8)alquilo, ciano(C1-C8) alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2-C8) alquenilo, hidroxi(C1-C8)alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (hidroxi(C1-C8)alquil-)tio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (C1-C8)alcoxi(C1-C8)alquilo, ((C1-C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1- C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, amino(C1-C8)alquilamino, (heterociclilo de 3 a 15

miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino, ((C3-C10) cicloalquil(C1-C8)alquil)amino, alquilcarbonilamino, (C1-C8) alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquil-carbonilamino, (C1-C8)alcoxi(C1-C8)alquilcar-bonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, ((C1-C8) alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8)alquilsulfonilamino, amino(C1- C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8) alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)al-quilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1- C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-

C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, ((C3-C10) cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)al-quil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonyt(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, (C1-C8) alcoxi(C1-

C8)alquilcarboniloxi(C1-C8)alquilo, di(C1-C8) alquilaminocarboniloxi(C1-C8)alquilo, (C1-C8)alquilcarbonil(C1-C8)al-quilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8) alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonilo, (aminocarbonil(C1-C8)al-quil)aminocarbonilo, (mono(C1-C8) alquilaminocarbonil(C1-C8)alquil)aminocarbonilo, (carboxi(C1-C8)alquil) aminocarbonilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, amidino, hidroxiamidino, guanidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente

sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, monohalo(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, di(C1-C8)alquilureido, di(fenilo o naftilo opcionalmente sustituido)ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureidoalquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquil-carbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil) glicinamido,

(mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, glicinamido(C1-C8)alquilo, alaninamido, mono(C1-C8) alquilalaninamido, alaninamido(C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

o R^3 es

un sistema de anillo heterocíclico de 3-15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alquilsufonilo, (fenilo o naftilo

opcionalmente sustituido)sulfonilo, (C1-C8)alcoxi, hidroxi(C1-C8) alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, halo(C1-C8)alcoxi, (C2-C8) alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, amino, mono(C1- C8) alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8) alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil(C1-C8) alquil)amino, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, monoalquilamino(C1-C8)alquilo, di(C1- C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)

alcoxicarbonilamino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8) alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, guanidino, ureido, mono(C1- C8) alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, y glicinamido;

R^4 es

-O-, $-N(R^7)-$, $-C(R^8)_2-$ o un enlace;

R^5 es

una cadena (C1-C8) alquileno o una cadena (C1-C8) alquilideno, o, si R^4 es un enlace, R^5 es una cadena (C1-C8) alquilideno que se sustituye opcionalmente por (fenilo o naftilo opcionalmente sustituido) o $-N(R^7)_2$;

o R^4 y R^5 juntos son -HC=CH-

R^6 es

-C(O)-, -C(S)-, $-CH_2-$ o un enlace;

cada R^7

se selecciona en forma independiente entre el grupo formado por hidrógeno, (C1- C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alquilcarbonilo, (C1-C8) alquilcarbonil(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)(C1- C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8)alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8) alquilamino, di(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino,

(fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8) alquilcarbonil)((C1-C8)alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, cicloalquilcarbonilamino(C1-C8)alquilo, (C1- C8)alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil}((C1-C8)alquil) aminoalquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-

C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, carboxi(C1-C8) alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilamino-carbonil(C1-C8)alquilo, y di(C1-C8) alquilaminocarbonil(C1-C8)alquilo;

con la salvedad de que cuando R^4 es $-N(R^7)-$, R^3 no puede ser un sistema de anillo heterocíclico que contiene entre 4 y 8 miembros que consiste de átomos de carbono y sólo un átomo de nitrógeno; y con la salvedad de que cuando R^4 es $-C(R^8)_2$ o un enlace, R^3 no puede ser un sistema de anillo heterocíclico saturado con puente de 4-6 miembros que consiste de átomos de carbono y dos átomos de nitrógeno, y como único estereoisómero o una mezcla de los mismos; o una sal aceptable para uso farmacéutico de los mismos.

2. El uso de acuerdo con la reivindicación 1 de un compuesto como el definido en la reivindicación 1, en el que:

R^3 es

un sistema de anillo carbocíclico de 3 a 15 miembros sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto,

mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsulfonilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, (C1-C8)alquiltio(C1- C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8) alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi, halo(C1-C8)alcoxi, amino(C1-C8)alcoxi, (C3-C10)cicloalquilo, (C3- C10)cicloalquil(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino, (C3-C10)cicloalquilamino(C1-C8)alquilo, ciano(C1-C8) alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2-C8)alquenilo, hidroxi(C1-C8) alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (hidroxi(C1-C8)alquil)tio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (C1-C8)alcoxi(C1-C8)alquilo,

((C1-C8)alcoxi) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8) alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, amino(C1-C8)alquilamino, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, amino, ((C3-C10)cicloalquil(C1- C8)alquil) amino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)cicloalquil-carbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi-carbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil) ((C1-C8)alquil)amino, ((C1-C8)alcoxi-carbonil)((C1-C8)alquil)amino, (C1-C8) alquilsul-

fonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alco-

xicarbonilo, (C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, di(C1-C8) alquilaminocarboniloxi(C1-C8)alquilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8) alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (mono(C1-C8) alquilaminocarbonil(C1-C8)alquil)aminocarbonilo, (carboxi(C1-C8)alquil) aminocarbonilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-

C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, amidino, hidroxiamidino, guanidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, monohalo(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, di(C1-C8)alquilureido, di(fenilo o naftilo opcionalmente sustituido)ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido (C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-

C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, glicinamido(C1-C8)alquilo, alaninamido, mono(C1-C8) alquilalaninamido, alaninamido (C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo.

3. El compuesto de la reivindicación 2 en el que:

R^4 es

-O-, $-N(R^7)-$ o $-C(R^8)-$;

R^5 es

una cadena (C1-C8) alquileno;

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1- C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C3-C10)cicloal-quilcarbonilamino, (C3-C10)cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8)alquilsulfonilamino,

(fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcar-bonil)((C1-C8)alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8) alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil) ((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8)alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-

C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8) alquilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil4(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilamlnocarbonil(C1-C8)alquilo, y di(C1-C8)alquilaminocarbonil(C1-C8)alquilo.

4. El compuesto de la reivindicación 3 en el que:

R^4 es

-O-;

R^5 es

metileno; y

R^6 es

-C(O)-.

5. El compuesto de la reivindicación 4, en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8) alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2- C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, ciano(C1-C8)alquilo, halo(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo

opcionalmente sustituido)(C1-C8) alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8)alquilo, hidroxi(C1-C8) alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo;

R^3 es

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fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8) alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino,

amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalqui(C1-C8)alquil)amino(C1-C8)alquilo, (C1-CS)alcoxicarbonilamino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hi-

droxi(C1-C8) alcoxi) carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil) aminocarbonilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido) ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)al-

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quilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, y (3- 15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

6. El compuesto de la reivindicación 5 seleccionado del grupo formado por los siguientes compuestos:

(2*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((fenoxi)metil)carbonil-2-etil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(metoximetil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-((acetilamino)metil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((4-fluorobencil)amino)etil)-4-(4-fluorobencil) piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((metil)amino)etil)-4- (4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-hidroxietil)amino)etil)-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-((((4-clorofenoxi)metil)carbonil)oxi)metil-5-metilpiperazina;

4- (4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(etoxicarbonil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(metoxicarbonil)metilpiperazina;

4-(4-fluorobencil)- 1-((4-clorofenoxi)metil)carbonil-3-((metoxi)metil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-(metoxi) etil)piperazina;

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4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxi-2-(4-metilfenil)etil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxipropil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxibut-4-inil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-5-(2-hidroxi-2-metilpropil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(2- hidroxietil)piperazina ;

1-((4-clorofenoxi)metil)carbonil-3-(2-((2-hidroxietil)amino)etil)-4-(4-fluorobencil)piperazina;

(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,3- dimetilpiperazina;

(2*S*,5*R*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-(2-metiltio)etilpiperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5- (benciloxi)metilpiperazina;

(2*R*,5*R*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-(((2-hidroxietil)tio)metil)piperazina;

4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-2-(*N'*-(etoxicarbonilmetil) ureido) metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((amino)carboniloxi)metil-4-(4-fluorobencil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-((acetil)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1-hidroxi-1-(fenil)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-metil-5-(1-hidroxibutil)piperazina;

(2*R*,5 *S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((dietilamino)metil)piperazina;

(2*R*,5*S*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((dimetilamino)metil)piperazina;

(2*R*,5*S*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5- ((ciclopropil)amino)metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5 ((morfolin-4-il)metil)piperazina;

(2*R*,5*R*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((piperazin-1- il)metil)piperazina;

(*cis*)-1-((3,4,5-trimetoxifenoxi)metil)carbonil-2,6-dimetil-4-(4-fluorobencil)piperazina;

(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi)me-til)carbonil-2,6- dimetilpiperazina;

1-((fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((4- clorofenoxi)metil)carbonil-2-(2-hidroxipropil)-4-(4-fluorobencil) piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxibut-3-enil)-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil) carbonil-3-trifluorometil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-((4-(2,5-di(trifluorometil)fenilcarbonil)piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina.

7. El compuesto de la reivindicación 5, en el que: R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8)alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8) alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (heterociclilo

de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3- C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbo-nil-

amino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo,

(amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquil-ureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8) alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquil-glicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8) alquilcarbonil)((C1-C8)al-quil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)car-

bonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino-carbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbo-nil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo.

8. El compuesto de la reivindicación 7 seleccionado del grupo formado por los siguientes compuestos:

1-((3,4,5-trimetoxifenoxi)metil)carbonil-2- metil-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina;

(2*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)me-til)carbonil-2- propilpiperazina;

(2*S*)-4-(4-fluorobencil)-1-((4-

clorofenoxi)metil)carbonil-2-propilpiperazina;

4-(4-fluorobencil)-1-(((4-clorofenoxi)metil)carbonil)espiro[ciclopropan-1, 2'-piperazina];

1-((4-clorofenoxi)metil)carbonil-2- hidroximetil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1- ((4-clorofenoxi)metil)carbonil-2-(2-(metoxi)etil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-metilpropil)amino)etil) -4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

1-((4- clorofenoxi)metil)carbonil-4-(4-fluorobencil)-5-metilpiperazina;

(2*R*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

(2*S*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(hidroximetil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxietil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(((metil)ureido)metil)piperazina;

(2*R*,3*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2,3-dimetilpiperazina;

(*cis*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-(((4-clorofenoxi)metil)carbonil)oxi)etil-5-metilpiperazina;

(2 *R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5((hidroxi)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((metoxi)-metil)piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1-metiletil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-(1-hidroxietil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1- hidroxiprop-3-enil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((ciano) metil)piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi) metil)carbonil-2-metil-4-(4-fluorobencil)-5-((1,2,4-triazol-2-il)metil) piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)-5-((tetrazolil)metil)piperazina;

(3*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetilpiperazina;

1-((4-cloro-3- nitrofenoxi)metil)carbonil-2-metil-4-(4-

fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(dietilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-hidroxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-cloro-2-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((etil)(1-metilbutil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2- aminofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((4-cloro-3-nitrofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(bencilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((1-metilbutil)amino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*iso*-propilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diclorofenil)ureido)fe-

noxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(4-nitrofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(4-metilfenil)ureido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-bencilureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((ciclopropilmetil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(fenilaminometil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(acetilaminometil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((metilamino)(fenil)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(fenilsulfonil)(metil) aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(acetil)(metil)aminoetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-

fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(*N*-metil- *N'*-etilureido)etil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1- ((metil)(etil)amino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(dimetilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)-1-((4-cloro-2-((4-*t*- butoxicarbonilpiperazin-1-il)metil)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(oxazol-2- ilaminometil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

1-((4-cloro-2-(morfolin-4-ilmetil)fenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina;

(trans)-1- ((4-bromo-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-fluoro-3-clorofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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1-((4-cloro-2-metoxicarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-metoxicarbonilfenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-aminocarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-carboxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans)*-1-((3-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-metil-2-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-metil-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metoxicarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3- nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-acetil-2-(aminocarbonil)fenoxi)metil)

carbonil-2,5-dımetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-nitro-3-metilfenoxi)metil)carbonil-2,5-dımetil-4-(4- fluorobencil)piperazına;

(*trans*)-1-((5-nıtro-2-metılfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-amino-3-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5- nitro-2-aminofenoxi)metil)carbonil-2,5-dımetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((2-aminofenoxi)metil)carbonil-2, 5-dımetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3- metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-metoxi-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-metoxi-2-acetilfenoxi)metıl)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((2-((2-hidroxietil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencıl)pıperazına;

(*trans*)-1-((2-((2-hidroxietoxi)carbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(2-hidroxietoxi)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-acetil-4,5- dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-metoxi-2-(metoxicarbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(*N'*- metilureido)amino)metil)piperazina;

(*trans*)-1-((4- metil-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((3-cloro-5-metoxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metoxi-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-(hidroximetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2- (2-azidoetil)-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ftalimido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(maleimido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((4-(bencilcarbonil) piperazin-1-il)metil)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-((2,3, 4-trifluorofenil)aminocarbonil)piperazin-1-il)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-((2-fluorofenil)aminocarbonil)piperazin-1-il)metil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(2,6-difluorofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(etenilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ciclopropilcarbonilamino)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ciclopentilcarbonilamino)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((furan-2-il)carbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(fenilcarbonilamino)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-((*N'*-(3-metoxifenil)ureido)feno-

xi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(metoxicarbonilmetilcarbonil)-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(2-metoxicarboniletil)carbonil-*N'*-(metil)glicinamido)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-metilbencil)aminocarbonil- *N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-trifluorometil-4-fluorofenil)carbonil-*N'*-(metil)glicinamido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(4-metilbencil)aminocarbonil-*N'*-(metil)glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-clorofenil)carbonil-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(4-fluorobencil)aminocarbonil-*N'*-(metil)glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2-iodofenilcar-

bonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,3-difluorofenilcarbonil)glicinamido)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-((4-fenoxifenil)aminocarbonil)glicinamido)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diflurofenilcarbonil)glicinamido)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((2-iodofenilcarbonil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((etoxicarbonilmetilcarbonil)aminometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(3-cloropropil)ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2-fluoro-6-trifluorometilfenil)ureidometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((3-fluorofenil)carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-

fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2-(etoxicarbonil)etil)ureidometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((2,5-di(trifluorometil)fenil)carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-(*N'*-(2-(fenil)ciclopropil)ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

9. El compuesto de la reivindicación 7, en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8)alquilo y hidroxi(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8) alquilcarbonilamino,

halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1- C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8) alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil) ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcóxicarbonilamino(C1- C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

10. El compuesto de la reivindicación 9 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-((4-cloro-3-nitrofenoxi) metil)carbonil-2,5-

dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-2- (aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*S*,5*R*)-1-((4-bromo-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-1-((3-hidroxi-5-metilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2 *S*,5*R*)-1-((4-nitro-3-formilfenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(2R)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)car-bonil-2-(2-hidroxietil) piperazina;

(*trans*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5- dimetilpiperazina;

(*trans*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxietil)-5-metilpiperazina;

(2*R*,6*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2,6-dimetilpiperazina;

(*trans*)-1-((4-cloro-2- metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2-metil-4- (4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-3- (hidroximetil)fenoxi)me-til)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-hidroxietil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-aminofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-4-(4-fluorobencil)-1-((2-acetilamino-4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(*trans*)-1-((4-cloro-2-(propilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metoximetilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-(metoxicarbonil)etilcarbonilamino)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-etoxicarbonil)etilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metilsulfonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(bromometilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)-1-((4-cloro-2-(glicinamido) fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-metilglicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(alaninamido)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((aminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminocarbonil)(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-etiluredio)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(etilcarbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-amino-5-nitrofenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal diclorhidrato;

(*trans*)-1-((4-cloro-2-(((etil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((dietil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((ciclopropil)am-ino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((dimetil)amino)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(((metil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((amino)metil)fenoxi) metil)car-

bonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-metilpiperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(etilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(metilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(metilsulfonil)(metil)aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*)-1-((4-cloro-2-((piperazin-1-il)metil) fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-*t*-butoxicarbonilpiperazin-1-il) metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(imidazol-1-ilmetil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-

fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(imidazol-1-il)etil)fenoxi)metil)carbonil- 2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(triazol-1-ilmetilo)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(tetrazol-1-ilmetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((morfolin-4-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)-1-((4-cloro-2-aminocarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

1-((4-cloro-2-formilfenoxi)metil)carbonil-2- metil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4- cloro-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*)-1-((4-cloro-2-formilfenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metilaminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((aminocarbonilmetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((2-aminoetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4- aminocarbonilo fenilo opcionalmente sustituido)aminocarbonil)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(hidroxiamidino)fenoxi)metil) carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-((*N'*-(tricloromethilcarbonil) ureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(metoximetilcarbonil)glicinamido)fenoxi) metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-(*N'*-(etoxicarbonyiaminocarbonil) glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina.

11. El compuesto de la reivindicación 9, en el que R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y en la posición 2 por aminocarbonilo, ureido, o

glicinamido; a saber, el compuesto seleccionado del grupo formado por los siguientes compuestos:

(2*R*,5*S*)-1-((4-cloro-2- (aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(glicinamido)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)- 1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(ureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*, 5*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina; y

(2*R*,5*S*)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

12. El compuesto de la reivindicación 9 en el que el compuesto más preferido es:

(2*R*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

13. El compuesto de la reivindicación 3 en el que:

R^4 es

-N(R^7)-;

R^5 es

metileno;

R^6 es

-C(O)-; y

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo.

14. El compuesto de la reivindicación 13 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8) alquiltio(C1-C8)alquilo,

hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8) alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8) alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, hidroxi(C1-C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo;

R^3 es

fenilo que se sustituye opcionalmente por uno o más

sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8) alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8)alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8) alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8) alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo,

mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ((C1-C8) alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre) amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi) carbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo,

(aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil) aminocarbonilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil) glicinamido, (aminocarbonil)((C1-C8) alquil)glicina-mido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente

sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre) (C1-C8)alquilo.

15. El compuesto de la reivindicación 14 en elque:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1- C8) alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo,

(fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8) alcoxi, (C3-C10)cicloalquil-amino(C1-C8)alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido) (c1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)al-quilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(c1- C8)al-quilamino, (C1-C8)alquilcarbonilamino, (C2-C8)alque-nilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de

nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)al-

quil)aminocarbonilo, (hidroxi(C1-C8)al-quil)amino-carbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8) alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8) alquilcarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente

sustituido)carbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(c1-C8) alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

16. El compuesto de la reivindicación 15 en elque:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8) alquilo y hidroxi(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-

C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (3C-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8) alquilcarbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8)alquil-sulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8) alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil) ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1- C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

17. El compuesto de la reivindicación 16 en el que

R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido.

18. El compuesto de la reivindicación 17 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-((4-clorofenilamino)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(aminocarbonil)fenilamino)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina; y

1-((4-clorofenilamino)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina.

19. El compuesto de la reivindicación 3 en el que:

R^4 es

$-C(R^8)_2-$;

R^5 es

metileno;

R^6 es

$-C(O)-$; y

cada R^8

se selecciona en forma independiente entre el grupo formado por hidrógeno, (C1- C8) alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8)

alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre) carbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1- C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, y di(C1-C8)alquilamino(C1- C8)alquilo.

20. El compuesto de la reivindicación 19 en el que: R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidr-

oxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8) alquiltio(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8) alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil) ureido(C1-C8)alquilo, hidroxi(C1- C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos

seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo;

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8) alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno,

oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di (C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a

15 miembros

que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8) alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8) alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil) aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, di(C1-C8) alquilaminocarbonil(C1-C8) alquilo, hidroxiamidino, ureido, mono(C1-C8) alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)urei-

do(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (3-15membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

21. El compuesto de la reivindicación 20 en el que: R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8) alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (3- 15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10)ciclo-alquilamino(C1-C8) alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquil-amino, di(C1-C8) alquilamino, mono(fenilo o naftilo

opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil) amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino (C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquil-carbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o

naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo; (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil) ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-

C8)alquilcarbo-nil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)al-quilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)car-bonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno,oxígeno y azufre)(C1-C8)alquilo.

22.El compuesto de la reivindicación 21 en el que: R^{1a} es

uno o más sustituyentes seleccionados entre el grupo

formado por (C1-C8) alquilo y hidroxi(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8)alquilcarbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8) alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8) alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1- C8)alquilcarbonil)glicinamido,

(aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

23. El compuesto de la reivindicación 22 en el que:

R^2 es

4- fluoro;

R^3 es

fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido; y

un R^8 es

hidrógeno y el otro R^8 es seleccionado del grupo formado por amino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo,

(heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre) carbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, y amino(C1-C8)alquilo.

24. El compuesto de la reivindicación 23 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-(2-(4-clorofenil)-3- (metilsulfonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(acetilamino) propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(metilsulfonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(acetilamino)etil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(amino)etil)carbonil-2,5-

dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(ureido)etil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-amino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*t*-butoxicarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((etoxicarbonilmetilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-*iso*-propil-ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-(2-cloroetil)ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2-nitrofenil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((4-metoxifenilmetil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2,4-dinitrofenil)sulfonilamino)etil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(ciclopropilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2-ciclopropiletil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-((2-metilpropil)carbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(cicloppentilcarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(*t*-butil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(etil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(3-choropropil) ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-(2-(4-clorofenil)-3-((morfolin-4-

il)carbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

25. El compuesto de la reivindicación 1 en el que:

R^3 es

un sistema de anillo heterocíclico sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8) alquilo, (C1-C8)alquilsulfonilo, (fenilo o naftilo opcionalmente sustituido) sulfonilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, halo(C1-C8) alcoxi, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido) (C1-C8)alquilamino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)ci-cloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, ((C1-C8)alcoxicarbonil)((C1-

C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8) alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, guanidino, ureido, mono(C1- C8) alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, y glicinamido.

26. El compuesto de la reivindicación 25 en el que: R^4 es

-O-, - N(R^7)- o -C(R^8)-;

R^5 es

una cadena (C1-C8) alquileno;

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10)cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino,

(C1-C8)alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonil)((C1-C8)alquil)amino, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1- C8)alquilo, mono(C1-

C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, carboxi(C1-C8) alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo,y di(C1-C8) alquilaminocarbonil(C1-C8)alquilo.

27. El compuesto de la reivindicación 26 en el que:

R^4 es -O-;

R^5 es metileno; y

R^6 es -C(O)-.

28. El compuesto de la reivindicación 26 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8) alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8)alquilo,

hidroxi(C1-C8) alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, hidroxi(C1- C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo; y

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo.

29. El compuesto de la reivindicación 28 R^3 seleccionado del grupo formado por azepinilo, acridinilo,

bencimidazolilo, benzotiazolilo, benzoxazolilo, benzopiranilo, benzopiranonilo, benzofuranilo, benzofuranonilo, benzotienilo, carbazolilo, cinnolinilo, decahidroisoquinolilo, dioxolanilo, furilo, isotiazolilo, quinuclidinilo, imidazolilo, imidazolinilo, imidazolidinilo, isotiazolidinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, indanilo, indolizinilo, isoxazolilo, isoxazolidinilo, morfolinilo, naftiridinilo, oxadiazolilo, octahidroindolilo, octahidroisoindolilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxoazepinilo, oxazolilo, oxazolidinilo, piperazinilo, 4- piperidonilo, fenazinilo, fenotiazinilo, fenoxazinilo, ftalazinilo, pteridinilo, purinilo, pirrolilo, pirazolilo, pirazolidinilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, quinazolinilo, quinoxalinilo, quinolinilo, quinuclidinilo, isoquinolinilo, tiazolilo, tiazolidinilo, tiadiazolilo, triazolilo, tetrazolilo, tetrahidrofurilo, tetrahidropiranilo, tienilo, tiamorfolinilo, tiamorfolinilo sulfóxido, y tiamorfolinilsulfona.

30. El compuesto de la reivindicación 29 en el que R^3 es benzopiranilo, benzopiranonilo, benzfuranilo, benzofuranonilo, quinolinilo, indolilo, indolinilo, oxazolilo, imidazolilo, o benzotienilo.

31. El compuesto de la reivindicación 30, a saber: (*trans*)-1-((benzo[b]piran-2-on-7- iloxi)metil)carbonil-2,5-

dimetil-4-(4-fluorobencil)piperazina.

32. Los compuestos

(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpiperazin-1-il]-3-oXopropenil]- fenil)-urea,

N-(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpiperazin-1-il]-3- oxopropenil] fenil)-metansulfonamida,

(5-Cloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobencil)-2,5-dimetilpiperazin-1-il]-3-oxopropenil]-fenil)-urea,

N-(5-Cloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobencil)-2, 5-dimetilpiperazin-1-il]-3-oxopropenil]-fenil)-metansulfonamida,

metiléster de ácido (5-Cloro-2- {(E)-3-[4-(4-fluorobencil)-2-metil-piperazin-1-il]-3-oxo-propenil}-fenil)-acético,

ácido 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxo-propenil}- benzoico,

(5-cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxo-propenil}-4-metoxi-fenil)-urea,

(5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxopropenil}-4-trifluorometoxi-fenil)-urea,

metiléster de ácido 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oXo-propenil}-4-metoxi-benzoico

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-

piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-propiónico,

ácido (5-Cloro-2-{2-[4-(3,4-difluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[4-(4-cloro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Cloro-2-{2-[4- (4-cloro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[4-(3, 4-difluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acé-tico,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxv}-fenil)-acrílico,

N-[(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acetil]-

metansulfonamida,

N-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-benzoil)-metansulfonamida,

N- [(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acetil]-C,C,C-trifluoro-metansulfonamida,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-oxo-acético,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)- acético,

ácido 2-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-ill-2-oxo-etoxi}-fenoxi)-2-metil- propiónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)-difluoro-acético

(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfonamida

N-[5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]fenil-trifluorometansulfonamida,

5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-bencensulfonamida.

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5- Bromo -2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-etansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfónico,

monoetiléster de ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R, 5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil) fosfónico,

ácido 5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfonamídico

metiléster de ácido 5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético;

metiléster de ácido 5-bromo-2-[2-[(2*R*)-4-[(4- fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metilbenzoico;

metiléster de ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico;

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-(trifluorometil)benzoico;

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-

[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]benzoico;

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*)-4-[(5-cloro-2-tienil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencensulfónico;

ácido 5-cloro-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencensulfónico;

ácido 5-cloro-4-(dimetilamino)-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético

ácido 5-bromo-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencen acético;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metil- benzoico

ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico.

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-(trifluorometil) benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxi-benzoico;

ácido 5-cloro-4-etoxi-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 4-amino-5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 4-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-

dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-5-metil benzoico

en la producción de un medicamento para el tratamiento y la prevención de la endometrosis en seres humanos

33 Uso de una composición farmacéutica que comprende una cantidad eficaz en términos terapéuticos de un compuesto como el descripto en cualquiera de las reivindicaciones 1 a 32 en la confección de un envase de medicamento para el tratamiento y la prevención de endometrosis en humanos.

Este requerimiento debe ser presentado directamente en el Organismo de Examen Internacional Preliminar competente o, si dos o mas organismos son competentes, en aquel elegido por el solicitante En la linea de abajo debe ser indicado el nombre completo o el codigo de dos letras de tal organismo

IPEA/ _____

PCT

CAPÍTULO II

REQUERIMIENTO

Segun el artículo 31 del Tratado de Cooperación Internacional en Materia de Patentes
El(Los) abajo firmante(s) requiere(n) que la solicitud internacional especificada abajo sea sometida a un examen internacional preliminar de acuerdo con el Tratado de Cooperacion Internacional en Materia de Patentes

A completar por el Organismo de Examen Internacional Preliminar

Identificación de IPEA	Fecha de recepcion de la SOLICITUD

Campo N° 1 IDENTIFICACION DE LA SOLICITUD INTERNACIONAL		Referencia del solicitante o agente *53139AWO*
Solicitud Internacional N° *PCT/EP 2008/002036*	Fecha de presentación internacional *(dia/mes/año)* *06 de diciembre de 2004* *23 02 2005*	Fecha de prioridad (mas temprana) *(dia/mes/año)* *10 de diciembre de 2003* *24 02 2004*

Titulo de la invencion

DERIVADOS DE PIPERAZINA PARA EL TRATAMIENTO DE ENDOMETROSIS

Campo N° 1 SOLICITANT(ES)

Apellido y nombre *(Apellido seguido de nombre, en una entidad legal, designación oficial completa La dirección debe incluir codigo postal y nombre de pais)*	Telefono N° *+49 30 468-192322*
SCHERING AKTIENGESELLSCHAFT *Mullerstrasse 178* *D-13353 Berlin* *ALEMANIA*	Facsimil N° *+49 30 468-12058*
	Teleprinter N°

Nacionalidad (*pais*)	Residencia (*pais*)
DE	*DE*

Apellido y nombre *(Apellido seguido de nombre, en una entidad legal, designación oficial completa La dirección debe incluir codigo postal y nombre de pais)*

KAUFMANN, Ulrike
Dorotheenstar 56
10117 Berlin
Alemania

Nacionalidad (*pais*)	Residencia (*pais*)
DE	DE

Apellido y nombre *(Apellido seguido de nombre, en una entidad legal, designación oficial completa La dirección debe incluir código postal y nombre de pais)*

HORUK, Richard
3410 Silver Spring Court
Lefayette, CA 94549, California 94549
U S A

Nacionalidad (*pais*)	Residencia (*pais*)
US	US

☐ Otros solicitantes estan indicados en una hoja de continuacion

Solicitud Internacional N°
PCT/EP 2005/0020236

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Campo N° III AGENTE O REPRESENTANTE COMUN, O DIRECCIÓN POSTAL

La siguiente persona es ☐ Agente ☐ Representante comun

y ☐ Ya ha sido designado anteriormente por el(los) solicitante(s) y (los) representa también para el Examen Preliminar Internacional

☐ es designado mediante la presente, una eventual designacion anterior de un agente/representante comun es revocada aqui

☐ es designado adicionalmente al agente/representante común designado anteriormente solo a los efectos del trámite ante el Organismo encargado del Examen Preliminar Internacional

Apellido y nombre *(Apellido seguido de nombre, en una entidad legal, designacion oficial completa La dirección debe incluir código postal y nombre de pais)*	Teléfono N°
JENAPHARM GmbH & Co KG *CRAMER, Eva-Maria* *Otto-Schott-Strasse 15* *DE - 07745 JENA*	*+49 30 468-192322*

☒ Marcar este casillero cuando no se indica(o) un agente representante comun, utilizando el espacio superior en lugar de indicar un domicilio especial al cual enviar la correspondencia

Campo N° IV BASES DEL EXAMEN PRELIMINAR INTERNACIONAL

Declaración acerca de modificaciones *

1 El solicitante desea que el Examen Preliminar Internacional se lleve a cabo basado sobre

☒ La Solicitud Internacional en la version original presentada

la descripcion ☐ en la version original presentada
☒ tomando en consideración las modificaciones segun el articulo 34

las reivindicaciones ☐ en la version original presentada
☐ tomando en consideración las modificaciones segun el articulo 19 (eventualmente junto con una declaración)
☒ tomando en consideracion las modificaciones segun el articulo 34

las ilustraciones ☐ en la version original presentada
☐ tomando en consideración las modificaciones segun el articulo 34

2 ☐ El solicitante desea que cada modificacion de las reivindicaciones presentadas segun el articulo 19 sea considerada como revisada

3 ☐ En caso de que, segun la regla 69 1 item b, el IPEA desee comenzar el examen preliminar internacional al mismo tiempo que la busqueda internacional, el solicitante requiere que el IPEA postergue el comienzo del examen preliminar internacional hasta la expiracion del plazo indicado por la regla 69 1 item d

4 ☐ El solicitante desea expresamente que el examen preliminar internacional comience ya antes la expiracion del plazo indicado por la regla 54*bis* 1 item a

* Cuando no se marca ningun casillero se comienza el examen preliminar internacional basado sobre la solicitud internacional en la version original presentada, cuando ingresa una copia de modificaciones de las reivindicaciones segun el articulo 19 y/o modificaciones de la solicitud internacional segun el articulo 34 ante el organismo encargado del examen preliminar internacional antes que el mismo presente un informe escrito o haya comenzado el informe de examen preliminar internacional, se utiliza sin embargo la version modificada

Idioma a los efectos del examen preliminar internacional: *inglés*

☒ es el idioma en el que fue presentada la solicitud internacional

☐ es el idioma de la traduccion que fue presentada a los efectos de la busqueda internacional

☐ es el idioma en el que fue publicada la solicitud internacional

☐ es el idioma de la traduccion que fue presentada / se presenta a los efectos del examen preliminar internacional

Campo N° V DESIGNACION DE ESTADOS COMO ESTADOS SELECCIONADOS

La presentacion de esta solicitud comprende la selección de todos los estados signatarios designados y que están vinculados mediante el capitulo II del PCT

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Hoja Nº 3

Solicitud Internacional Nº
PCT/EP 2005/002036

Campo Nº VI LISTADO DE VERIFICACIÓN

A la solicitud se le adjuntan los siguientes documentos en el idioma indicado en el campo Nº IV, a los efectos del examen preliminar internacional

A completar por el organismo encargado del examen preliminar internacional

				Recibida	No recibida
1	Traduccion de la solicitud internacional		hojas	☐	☐
2	Modificaciones segun articulo 34	57	hojas	☐	☐
3	Copia,(o, en caso de ser requerida, traduccion) de las modificaciones segun articulo 34		hojas	☐	☐
4	Copia,(o, en caso de ser requerida, traducción) de una declaracion segun articulo 19		hojas	☐	☐
5	Escrito adjunto	3	hojas	☐	☐
6	Otros (indicar individualmente)		hojas	☐	☐

A la solicitud se le adjuntan asimismo los siguientes documentos marcados

1	☒	Hoja de calculo de tasas	5	☐	Fundar la ausencia de una firma
2	☐	Original de un poder especial	6	☐	Protocolo de secuencias en forma electronica
3	☐	Original de un poder general	7	☐	Tablas en forma electronica relacionadas con un protocolo de secuencias
4	☐	Copia de poder general, Referencia en caso de existir	8	☐	Otros

Campo Nº VII FIRMA DEL SOLICITANTE, AGENTE O REPRESENTANTE COMÚN

Junto a cada firma se debe repetir el nombre de la persona firmante, debiendose indicar, en tanto no este indicado en la solicitud,, en que caracter firma la persona

SCHERING AKTIENGESELLSCHAFT

p p *p a*

(Firmado) *(Firmado)*

Dr T Seuß *A Bertucco*

A completar por el organismo encargando del examen preliminar internacional

1 Fecha del ingreso real de la SOLICITUD

2 Fecha de ingreso modificada de la solicitud como consecuencia de ENMIENDAS segun la regla 60 1 item b

3 ☐ La fecha de ingreso de la solicitud es POSTERIOR a 19 meses a partir de la fecha de prioridad, no corresponden los puntos 4 y 5 de abajo

☐ Se informo correspondientemente al solicitante

4 ☐ La fecha de ingreso de la solicitud se encuentra, como consecuencia de la prolongacion del plazo segun la regla 80 5, DENTRO de 19 meses a partir de la fecha de prioridad

5 ☐ La fecha de ingreso de la solicitud es posterior a la expiración de 19 meses a partir de la fecha de prioridad, pero su posterior ingreso es DISCULPADO segun la regla 82

6 ☐ La fecha de ingreso de la solicitud es POSTERIOR a la expiración del plazo prescripto por la regla 54*bis* 1 item 1, no corresponden los puntos 7 y 8 de abajo

7 ☐ La fecha de ingreso de la solicitud se encuentra, como consecuencia de la prolongacion del plazo segun la regla 80 5, DENTRO del plazo prescripto por la regla 54*bis* 1 item 1

8 ☐ La fecha de ingreso de la solicitud es posterior a la expiracion del plazo prescripto por la regla 54*bis* 1 item 1, pero su posterior ingreso es DISCULPADO según la regla 82

A completar por la Oficina Internacional

Solicitud recibida por IPEA el

Oficina de Patentes Europea
Dirección general 1

D – 80298 Munich

Schering AG
Corporate Patents
Müllerstr. 178
Berlín – Alemania

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Su referencia	Su carta del	Nuestra referencia (indicar en respuesta)	Fecha
PCT/EP 2005/002036		53189AWO	2005 12 23

Solicitud de patente internacional a nombre de Schering AG
Fecha de presentación internacional: 23.02.2005
Título: DERIVADOS DE PIPERAZINA PARA EL TRATAIENTO DE LA ENDOMETROSIS

Adición a la solicitud

Al EPO en su función de IPEA, enmiendas y argumentos según el artículo PCT 34

El solicitante se refiere al WOISA, de acuerdo con la regla 43*bis* 1 fecha 17 05 05 (Funcionario autorizado Johnson, C)

El solicitante remite nuevas páginas 3, 3a y 11 de la descripción y un nuevo juego de reivindicaciones, reemplazando así las páginas 3 y 11 de la descripción y las reivindicaciones como fueran presentadas originalmente

1. Las reivindicaciones recientemente presentadas

Las reivindicaciones 2 – 32 recientemente presentadas han sido enmendadas para cumplir la objeción de claridad del funcionario autorizado, insertando, en particular, el siguiente texto·

"2 El uso de acuerdo con la reivindicación 1 de un compuesto como el ~~descripto~~ definido en la reivindicación 1, en el que "

Además, la reivindicación 33 también ha sido enmendada, leyéndose ahora de la siguiente manera

"33 Uso de una composición farmacéutica ~~útil para el tratamiento de la endometrosis en un humano de sexo femenino que necesita dicho tratamiento,~~ que comprende una cantidad eficaz en términos terapéuticos de un compuesto ~~de acuerdo con la reivindicación 1~~ como el descripto en cualquiera de las reivindicaciones 1 a 32 en la confección de un envase de medicamento para el tratamiento y la prevención de endometrosis en humanos "

El soporte de las enmiendas se encuentra en la descripción, página 214, renglón 4, donde se describe un ejemplo de envase

La corrección de la página 11 de la descripción se refiere a un error de trascripción La WO 01/72728 debe ser la WO 0/102787, que es el documento en el cual están informados los compuestos particularmente favorables mencionados Tales compuestos acordes con la invención pueden ser utilizados en la manufactura de un medicamento para el tratamiento de la endometrosis

2. Los derivados de piperazina del documento 1 como antagonistas selectivos de CCR1, y el uso novedoso acorde con la presente solicitud en relación con el citado documento D2.

El solicitante reconoce positivamente la opinión del Funcionario autorizado resolviendo la novedad con respecto a D1 y D2 del objeto acorde con la presente solicitud

La EP 1254899 A describe derivados de piperazina antagonistas de la quimioquina humana "receptor C-C 1" (CCR1) en el tratamiento de un trastorno inflamatorio Los compuestos

descriptos en D1 se refieren a las quimioquinas MIP-1 y RANTES en el receptor CCR-, inhibiendo la actividad de tal quimioquina D1 ya está mencionada en la presente solicitud

De acuerdo con los datos que sustentan la presente invención, la infiltración de células inmunes en lesiones endometro-peritoneales muestra una expresión sobreregulada del receptor CCR1 Tales células inmunes, como por ejemplo, células macrofagas y células T, regulan el proceso inflamatorio La células inmunes que poseen tal expresión de CCR1 sobreregulada no son detectadas en el tejido endometrial (figuras 1 y 2)

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El solicitante hace notar respetuosamente al funcionario autorizado el hecho de que los antagonistas de CCR1 descriptos en la presente solicitud poseen un efecto directo y específico sobre la modulación del proceso inflamatorio a través del receptor CCR1 de las células inmunes de la lesión endometro-peritoneal y puede ser utilizado para el tratamiento específico de la endometrosis

La WO 2004002960 A (D2) describe derivados de piperazina en los cuales la piperazina está adjuntada a un anillo de quinolina Los compuestos de D2 están descriptos a modo de antagonistas selectivos para la quimioquina humana "receptor C-C 5" (CCR 5)

El funcionario autorizado remarca inmediatamente que el experto en la materia nunca selecciona compuestos con una estructura diferente y activa sobre un receptor distinto para proveer otros tratamientos para la endometrosis D2 enseña claramente en dirección contraria al uso de antagonistas selectivos de CCR-1 en el tratamiento de la endometrosis

Para cumplir los requisitos de la regla PCT 5(1)(ii), el documento D2 ha sido identificado en la nueva página 3as de la descripción, discutiendo el fundamento relevante de la técnica revelada en él De tal manera, hemos tomado particular cuidad en cumplir los requisitos del PCT en relación con la inserción de material nuevo

Creemos que, a la luz de las observaciones anteriores, las realizaciones descriptas en la reivindicación 1 presentada ahora son novedosas y originales, y no pueden ser derivadas de ningún otro documento mencionado en el informe de búsqueda internacional.

Al mismo tiempo, las nuevas reivindicaciones 2 a 33 deben ser consideradas novedosas y cumpliendo los requisitos de los artículos PCT 33(2) y 33(3)

El solicitante entiende que la solicitud está ahora en condiciones de lograr un Informe de Examen Preliminar Internacional positivo No obstante, en caso de existir otras objeciones mayores, estamos dispuestos a discutir el objeto de la presente solicitud directamente con el funcionario autorizado en una entrevista informal

Saludo de rigor

SCHERING AKTIENGESELLSCHAFT

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(Firmado	*(Firmado*
A Bertucco *Corporate Patents)*	Dr T Seuß Corporate Patent s

Adjunto nuevas páginas 3, 3a y 11 de la descripción, y un nuevo juego de las reivindicaciones

(Hoechst) describe derivados de piperazina que son útiles como agentes cardiotónicos. La solicitud publicada de patente europea 0 190 685 (G. D. Searle) describe derivados de piperazina que bloquean la vía metabólica de la 5-lipooxigenasa de la cascada del ácido araquidónico, y por lo tanto son útiles en el tratamiento de reacciones alérgicas y de hipersensibilidad e inflamación. La solicitud publicada de patente PCT, WO 96/34864 (Schering Plough) revela derivados de piperazina útiles como antagonistas de neuroquinina.

La solicitud publicada de patente europea 1 254 899 (Schering AG) revela los derivados de piperazina comprendidos en la presente solicitud para el tratamiento de un trastorno inflamatorio.

La solicitud de patente PCT WO 02/36581 (Schering AG) revela también derivados de piperazina comprendidos en la presente solicitud para el diagnóstico de la enfermedad de Alzheimer.

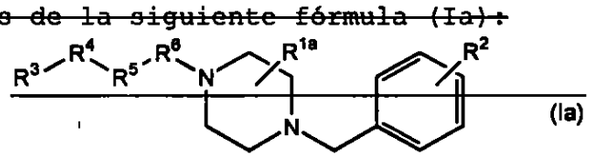
Todas las referencias anteriores se incorporan aquí en su totalidad como referencia.

Ninguna de las referencias anteriores describe los derivados de piperazina comprendidos en la presente solicitud para el tratamiento de la endometrosis en mujeres, donde dichos derivados de piperazina son antagonistas de Receptor 1 de Quimioquina Humana "C-C" (CCR1).

~~**RESUMEN DE LA INVENCIÓN**~~

~~Esta invención se relaciona con el uso de un compuesto de la siguiente fórmula (Ia) o su sal aceptable para uso farmacéutico para el tratamiento y prevención de la endometrosis en seres humanos en donde el tratamiento comprende administrar a un humano de sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de dicho compuesto.~~

~~De acuerdo con esto, en un aspecto, esta invención provee compuestos de la siguiente fórmula (Ia):~~



(Ia)

~~en donde:~~

~~R^{1a} es~~

~~uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por oxo, halo, alquilo, cicloalquilo, cicloalquilalquilo, cicloalquilaminoalquilo, (cicloalquilalquil)aminoalquilo, haloalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, formilo, formilalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, mercaptoalquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, (alcoxi)aralquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltioalquilo,~~

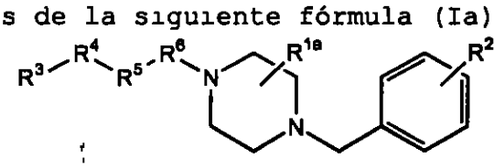
La WO 2004002960 A describe derivados de piperazina en los cuales la piperazina está adjuntada a un anillo de quinolina. Tales compuestos están descriptos a modo de antagonistas selectivos para la quimioquina humana "receptor C-C 5" (CCR 5). Según la WO 20054002960a, una de las condiciones de trastorno en las cuales está implicados los antagonistas de CCR5 es la endometrosis.

Los compuestos de la WO 2004002960 A poseen una estructura diferente y son activos sobre un receptor distinto.

RESUMEN DE LA INVENCIÓN

Esta invención se relaciona con el uso de un compuesto de la siguiente fórmula (Ia) o su sal aceptable para uso farmacéutico para el tratamiento y prevención de la endometrosis en seres humanos en donde el tratamiento comprende administrar a un humano de sexo femenino que necesita dicho tratamiento una cantidad eficaz en términos terapéuticos de dicho compuesto.

De acuerdo con esto, en un aspecto, esta invención provee compuestos de la siguiente fórmula (Ia):



(Ia)

en donde:

R^{1a} es

uno o más sustituyentes seleccionados en forma independiente entre el grupo formado por oxo, halo, alquilo, cicloalquilo, cicloalquilalquilo, cicloalquilaminoalquilo, (cicloalquilalquil)aminoalquilo, haloalquilo, alquenilo, alquinilo, arilo, aralquilo, aralquenilo, formilo, formilalquilo, hidroxialquilo, hidroxialquenilo, hidroxialquinilo, (hidroxi)aralquilo, (hidroxi)cicloalquilalquilo, mercaptoalquilo, cianoalquilo, haloalquilcarbonilaminoalquilo, (alcoxi)aralquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltioalquilo,

(C=ONH-(C1-C8)alquilo, (C1-C8)alquil-SO2-NH-(C1-C8)alquilo, (C2-C9)heteroaril-(C1-C8)alquilo, H2N-(C=O)-,H2N- (C=O)- (CI-C8) alquil-;

cada R4 se selecciona en forma independiente entre el grupo formado por: H-, HO-, halo-, NC-, HO-(C=O-, H2N-, (C1-C8)alquil-NH-, [(C1-C8)alquil]2N-, (C1-C8)alquil-opcionalmente sustituido con 1-3 átomos de flúor,(C1-C8) alquil-O- en donde el grupo alquilo es opcionalmente sustituido con 1-3 átomos de flúor, HO-(C1-C8)alquil-, (C1-C8)alquil-O-(C1-C8)alquil-, H2N-(C1-C8)alquil-, (C1-C8)alquilo NH-(C1-C8)alquil-, [(C1-C8)alquil]2N-(C1-C8)alquil-, (C1-C8)alquil-(C=O)-, (C1-C8)alquil-(C=O)-(CC8) alquil-, (C6-C10)aril-, (C2-Cg) heteroaril-, (C6-C10) ariloxi, H2N-(C=O), H2N-(C=O)-(CC8) alquilo, (C1-C8)alquil-NH-(C=O)-, (C1-C8)alquil-NH-(C=O)-(C1-C8)alquil-, [(C1-C8)alquil]2N (C=O)-, [(C1-C8)alquil]2-N-(C=O)-(C1-C8)alquil-, (C3-C8)cicloalquil-, (C1-C8)alquil-SO2-, NC-(C C8)alquil-, (C1-C8) alquil-(C=O)-NH-, H2N-(C=O)-NH-, H2N-(C=O)-NH-(C1-C8) alquil-;

R5 es (C1-C8) alquil-.

para el tratamiento y prevención de la endometrosis.

Algunas realizaciones particularmente favorables de la presente invención son los siguientes compuestos según se informan en ~~WO01/72728~~ WO02/102787:

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-me-til-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5- Bromo -2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- etansulfónico,

|La solicitud de patente WO2004/055031 en su totalidad se incorpora por referencia a la presente solicitud. Algunas formas de realización ventajosas de acuerdo con la presente invención son los compuestos de la fórmula I- WO2004/055031

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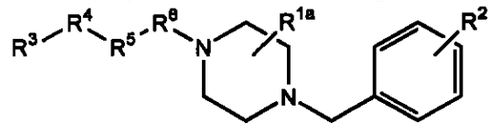
REIVINDICACIONES

1. Uso de un compuesto de la siguiente fórmula (Ia):



(Ia)

en la producción de un medicamento para el tratamiento y la prevención de la endometrosis en seres humanos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por oxo, halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, ((C3-C10)cicloalquil(C1-C8)alquil) amino(C1-C8)alquilo, halo(C1-C8)alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2- C8)alquenilo, formilo, formil(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, mercapto(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-

C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8) alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8) alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, azido(C1-C8)alquilo, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8) alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo,

(fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8) alquilo, (C1-C8)alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a

15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto, mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsufonilo, (C1- C8)alquiltio(C1-C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8) alquilsulfonil(C1-C8)alquilo, (C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi, halo(C1-C8) alcoxi, (C3-C10)cicloalquilo, (C3-C10)cicloalquil(C1-C8)alquilo, (hidroxi)(C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino, (C3-C10) cicloalquilamino(C1-C8)alquilo, ((C3-C10)cicloalquil(C1-C8)alquil)amino, ((C3-C10)cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, ciano(C1-C8)alquilo, (C2-C8) alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo

opcionalmente sustituido)(C2-C8)alquenilo, hidroxi(C1-C8)alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8) alquinilo, (C1-C8)alcoxi(C1-C8)alquilo, ((C1-C8)al-coxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1- C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8) alquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino, ((C1-C8) alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8)al-

coxicarbonilamino(C1-C8) alquilo, ((C1-C8)alcoxi-carbonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcox-icarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxicarbonilo, (C1-C8)alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbony((C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilami-nocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)al-quilaminocarbonil(C1- C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C7-C8) alquilaminocarbonil(C1-

C8)alquilo, amidino, guanidino, ureido, mono(C1-C8) alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (3-15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^3 es

un sistema de anillo carbocíclico de 3 a 15 miembros sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto, mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsufonilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, (C1-C8)alquiltio(C1- C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8) alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo

opcionalmente sustituido)(C1-C8) alcoxi, halo(C1-C8)alcoxi, amino(C1-C8)alcoxi, (C3-C10)cicloalquilo, (C3- C10)cicloalquil(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino, (C3-C10)cicloalquilamino(C1-C8)alquilo, ciano(C1-C8) alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2-C8) alquenilo, hidroxi(C1-C8)alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (hidroxi(C1-C8)alquil-)tio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (C1-C8)alcoxi(C1-C8)alquilo, ((C1-C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1- C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, amino(C1-C8)alquilamino, (heterociclilo de 3 a 15

miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino, ((C3-C10) cicloalquil(C1-C8)alquil)amino, alquilcarbonilamino, (C1-C8) alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquil-carbonilamino, (C1-C8)alcoxi(C1-C8)alquilcar-bonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, ((C1-C8) alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8)alquilsulfonilamino, amino(C1- C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8) alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)al-quilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1- C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-

C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, ((C3-C10) cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)al-quil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonyt(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, (C1-C8) alcoxi(C1-

C8)alquilcarboniloxi(C1-C8)alquilo, di(C1-C8) alquilaminocarboniloxi(C1-C8)alquilo, (C1-C8)alquilcarbonil(C1-C8)al-quilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8) alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonilo, (aminocarbonil(C1-C8)al-quil)aminocarbonilo, (mono(C1-C8) alquilaminocarbonil(C1-C8)alquil)aminocarbonilo, (carboxi(C1-C8)alquil) aminocarbonilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, amidino, hidroxiamidino, guanidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente

sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, monohalo(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, di(C1-C8)alquilureido, di(fenilo o naftilo opcionalmente sustituido)ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureidoalquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquil-carbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil) glicinamido,

(mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, glicinamido(C1-C8)alquilo, alaninamido, mono(C1-C8) alquilalaninamido, alaninamido(C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

o R^3 es

un sistema de anillo heterocíclico de 3-15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alquilsufonilo, (fenilo o naftilo

opcionalmente sustituido)sulfonilo, (C1-C8)alcoxi, hidroxi(C1-C8) alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, halo(C1-C8)alcoxi, (C2-C8) alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, amino, mono(C1- C8) alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8) alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil(C1-C8) alquil)amino, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, monoalquilamino(C1-C8)alquilo, di(C1- C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)

alcoxicarbonilamino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8) alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, guanidino, ureido, mono(C1- C8) alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, y glicinamido;

R^4 es

-O-, $-N(R^7)-$, $-C(R^8)_2-$ o un enlace;

R^5 es

una cadena (C1-C8) alquileno o una cadena (C1-C8) alquilideno, o, si R^4 es un enlace, R^5 es una cadena (C1-C8) alquilideno que se sustituye opcionalmente por (fenilo o naftilo opcionalmente sustituido) o $-N(R^7)_2$;

o R^4 y R^5 juntos son -HC=CH-

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R^6 es

-C(O)-, -C(S)-, $-CH_2-$ o un enlace;

cada R^7

se selecciona en forma independiente entre el grupo formado por hidrógeno, (C1- C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alquilcarbonilo, (C1-C8) alquilcarbonil(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)(C1- C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8)alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8) alquilamino, di(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino,

(fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8) alquilcarbonil)((C1-C8)alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, cicloalquilcarbonilamino(C1-C8)alquilo, (C1- C8)alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) aminoalquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-

C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, carboxi(C1-C8) alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilamino-carbonil(C1-C8)alquilo, y di(C1-C8) alquilaminocarbonil(C1-C8)alquilo;

con la salvedad de que cuando R^4 es $-N(R^7)-$, R^3 no puede ser un sistema de anillo heterocíclico que contiene entre 4 y 8 miembros que consiste de átomos de carbono y sólo un átomo de nitrógeno; y con la salvedad de que cuando R^4 es $-C(R^8)_2$ o un enlace, R^3 no puede ser un sistema de anillo heterocíclico saturado con puente de 4-6 miembros que consiste de átomos de carbono y dos átomos de nitrógeno, y como único estereoisómero o una mezcla de los mismos; o una sal aceptable para uso farmacéutico de los mismos.

2. El uso de acuerdo con la reivindicación 1 de un compuesto como el definido en la reivindicación 1, en el que:

R^3 es

un sistema de anillo carbocíclico de 3 a 15 miembros sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, hidroxisulfonilo, halo, (C1-C8)alquilo, mercapto,

mercapto(C1-C8) alquilo, (C1-C8)alquiltio, (C1-C8)alquilsulfinilo, (C1-C8)alquilsulfonilo, (fenilo o naftilo opcionalmente sustituido)sulfonilo, (C1-C8)alquiltio(C1- C8)alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8) alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, (fenilo o naftilo opcionalmente sustituido)oxi, halo(C1-C8)alquilo, formilo, formil(C1-C8)alquilo, nitro, nitroso, ciano, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi, halo(C1-C8)alcoxi, amino(C1-C8)alcoxi, (C3-C10)cicloalquilo, (C3- C10)cicloalquil(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino, (C3-C10)cicloalquilamino(C1-C8)alquilo, ciano(C1-C8) alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2-C8)alquenilo, hidroxi(C1-C8) alquilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (hidroxi(C1-C8)alquil)tio(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (C1-C8)alcoxi(C1-C8)alquilo,

((C1-C8)alcoxi) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8) alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, amino(C1-C8)alquilamino, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, amino, ((C3-C10)cicloalquil(C1- C8)alquil) amino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)cicloalquil-carbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi-carbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil) ((C1-C8)alquil)amino, ((C1-C8)alcoxi-carbonil)((C1-C8)alquil)amino, (C1-C8) alquilsul-

fonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alco-

xicarbonilo, (C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonil(C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, di(C1-C8) alquilaminocarboniloxi(C1-C8)alquilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8) alquilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (mono(C1-C8) alquilaminocarbonil(C1-C8)alquil)aminocarbonilo, (carboxi(C1-C8)alquil) aminocarbonilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-

C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil(C1-C8)alquilo, amidino, hidroxiamidino, guanidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, monohalo(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, di(C1-C8)alquilureido, di(fenilo o naftilo opcionalmente sustituido)ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido (C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-

C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, glicinamido(C1-C8)alquilo, alaninamido, mono(C1-C8) alquilalaninamido, alaninamido (C1-C8)alquilo, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo.

3. El compuesto de la reivindicación 2 en el que:

R^4 es

-O-, $-N(R^7)-$ o $-C(R^8)-$;

R^5 es

una cadena (C1-C8) alquileno;

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1- C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C3-C10)cicloal-quilcarbonilamino, (C3-C10)cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8)alquilsulfonilamino,

(fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcar-bonil)((C1-C8)alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8) alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil) ((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8)alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-

C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8) alquilo, carboxi(C1-C8)alquilo, (C1-C8)alcoxicarbonil4(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilamlnocarbonil(C1-C8)alquilo, y di(C1-C8)alquilaminocarbonil(C1-C8)alquilo.

4. El compuesto de la reivindicación 3 en el que:

R^4 es

-O-;

R^5 es

metileno; y

R^6 es

-C(O)-.

5. El compuesto de la reivindicación 4, en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8) alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2- C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, ciano(C1-C8)alquilo, halo(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo

opcionalmente sustituido)(C1-C8) alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8)alquilo, hidroxi(C1-C8) alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo;

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8) alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino,

amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalqui(C1-C8)alquil)amino(C1-C8)alquilo, (C1-CS)alcoxicarbonilamino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionálmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8)alquilo,. carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hi-

droxi(C1-C8) alcoxi) carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil) aminocarbonilo, di(C1-C8)alquilamino-carbonil(C1-C8)alquilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido) ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)al-quilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicar-bonil(C1-C8)alquil)ureido(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)al-quilcarbonil)glicinamido, (aminocarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)al-

quilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, y (3- 15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

6. El compuesto de la reivindicación 5 seleccionado del grupo formado por los siguientes compuestos:

(2*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((fenoxi)metil)carbonıl-2-etil-4-(4-fluorobencil)pıperazına;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpıperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(metoximetil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-((acetilamino)metil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((4-fluorobencıl)amıno)etıl)-4-(4-fluorobencil) piperazina;

1-((4-clorofenoxi)metıl)carbonil-2-(2-((metil)amino)etil)-4- (4-fluorobencil)piperazına;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-hidroxietil)amino)etil)-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxı)metil)carbonil-3-((((4-clorofenoxı)metil)carbonil)oxi)metil-5-metılpıperazına;

4- (4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(etoxıcarbonıl) piperazına;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(metoxicarbonil)metılpiperazina;

4-(4-fluorobencil)- 1-((4-clorofenoxi)metil)carbonil-3-((metoxı)metıl)pıperazina;

4-(4-fluorobencil)-1-((4-clorofenoxı)metıl)carbonil-3-(2-(metoxi) etil)pıperazina;

4-(4-fluorobencıl)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxi-2-(4-metilfenil)etil)piperazina;

4-(4- fluorobencıl)-1-((4-clorofenoxi)metil)carbonil-3-(2-hidroxipropil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonıl-3-(2-hidroxibut-4-ınil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-5-(2-hidroxi-2-metilpropil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxı)metil)carbonil-3-(2- hidroxietil)piperazına ;

1-((4-clorofenoxi)metil)carbonil-3-(2-((2-hidroxi-etil)amino)etil)-4-(4-fluorobencil)piperazina;

(*cis*)-4-(4-fluorobencil)-1-((4-clorofeno-xı)metıl)carbonıl-2,3- dımetilpıperazina;

(2*S*,5*R*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dımetıl-4-(4-fluorobencıl) pıperazına;

(2*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(2*R*,5*S*)-4-(4-fluorobencıl)-1-((4-clorofenoxı)metil)carbonil-2- metil-5-(2-metiltio)etilpiperazina;

(2*R*,5*R*)-4-(4-fluorobencıl)-1-((4-clorofenoxi)metil)carbonil-2-metil-5- (benciloxi)metilpiperazina;

(2*R*,5*R*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-(((2-hidroxietil)tıo)metıl)piperazina;

4-(4-fluorobencil)-1-((4- clorofenoxi)metil)carbonil-2-(*N'*-(etoxicarbonilmetil) ureido) metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((amino)carboniloxi)metil-4-(4-fluorobencil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-((acetil)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1-hidroxi-1-(fenil)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-metil-5-(1-hidroxibutil)piperazina;

(2*R*,5 *S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((dietilamino)metil)piperazina;

(2*R*,5*S*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((dimetilamino)metil)piperazina;

(2*R*,5*S*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5- ((ciclopropil)amino)metil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5 ((morfolin-4-il)metil)piperazina;

(2*R*,5*R*)-1-((4- clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((piperazin-1- il)metil)piperazina;

(*cis*)-1-((3,4,5-trimetoxifenoxi)metil)carbonil-2,6-dimetil-4-(4-fluorobencil)piperazina;

(*cis*)-4-(4-fluorobencil)-1-((4-clorofenoxi)me-til)carbonil-2,6- dimetilpiperazina;

1-((fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((4- clorofenoxi)metil)carbonil-2-(2-hidroxipropil)-4-(4-fluorobencil) piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxibut-3-enil)-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil) carbonil-3-trifluorometil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-((4-(2,5-di(trifluorometil)fenilcarbonil)piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina.

7. El compuesto de la reivindicación 5, en el que: R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8)alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8) alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (heterociclilo

de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3- C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbo-nil-

amino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo,

(amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquil-ureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)• alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8) alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquil-glicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8) alquilcarbonil)((C1-C8)al-quil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)car-

bonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino-carbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbo-nil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8) alquilo.

8. El compuesto de la reivindicación 7 seleccionado del grupo formado por los siguientes compuestos:

1-((3,4,5-trimetoxifenoxi)metil)carbonil-2- metil-4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-etilpiperazina;

(2*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)me-til)carbonil-2- propilpiperazina;

(2*S*)-4-(4-fluorobencil)-1-((4-

clorofenoxi)metil)carbonil-2-propilpiperazina;

4-(4-fluorobencil)-1-(((4-clorofenoxi)metil)carbonil)espiro[ciclopropan-1, 2'-piperazina];

1-((4-clorofenoxi)metil)carbonil-2- hidroximetil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1- ((4-clorofenoxi)metil)carbonil-2-(2-(metoxi)etil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2-(2-((2-metilpropil)amino)etil) -4-(4-fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

1-((4- clorofenoxi)metil)carbonil-4-(4-fluorobencil)-5-metilpiperazina;

(2*R*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

(2*S*)-1-((4-clorofenoxi)metil)carbonil-3-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-3-(hidroximetil) piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3-(2-hidroxietil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(((metil)ureido)metil)piperazina;

(2*R*,3*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2,3-dimetilpiperazina;

(*cis*)-1-((4-clorofenoxi)metil)carbonil-3,5-dimetil-4-(4-fluorobencil)piperazina;

4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-(((4-clorofenoxi)metil)carbonil)oxi)etil-5-metilpiperazina;

(2 *R*,5*R*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5((hidroxi)metil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-((metoxi)-metil)piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2-metil-5-(1-metiletil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2- metil-5-(1-hidroxietil)piperazina;

(2*R*,5*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-metil-5-(1- hidroxiprop-3-enil)piperazina;

(2*R*,5*S*)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)-5-((ciano) metil)piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi) metil)carbonil-2-metil-4-(4-fluorobencil)-5-((1,2,4-triazol-2-il)metil) piperazina;

(2*R*,5*R*)-1-((4-clorofenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)-5-((tetrazolil)metil)piperazina;

(3*S*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-3,5-dimetilpiperazina;

1-((4-cloro-3- nitrofenoxi)metil)carbonil-2-metil-4-(4-

fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(dietilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-hidroxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-cloro-2-metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((etil)(1-metilbutil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2- aminofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

1-((4-cloro-3-nitrofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(bencilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((1-metilbutil)amino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*iso*-propilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diclorofenil)ureido)fe-

noxi) metil)carbonil-2,5-dimetil-4-(4-fluoroben-
cil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(4-nitrofenil)ureido)feno-
xi)metil)carbonil-2,5-dimetil-4-(4-fluoroben-
cil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(4-metilfenil)ureido)
fenoxi)metil)carbonil-2,5-dimetil-4-(4-
fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-bencilureido)fenoxi)metil)
carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((ciclopropilmetil)aminometil)fe-
noxi)metil)carbonil-2,5-dimetil-4-(4-
fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(fenilaminometil)fenoxi)metil)
carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(acetilaminometil)fenoxi)metil)
carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((metilamino)(fenil)metil)fenoxi)
metil)carbonil-2,5-dimetil-4-(4-
fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(fenilsulfonil)(metil)
aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-
fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(acetil)(metil)aminoetil)
fenoxi)metil)carbonil-2,5-dimetil-4-(4-

fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(*N*-metil- *N'*-etilureido)etil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1- ((metil)(etil)amino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(dimetilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)-1-((4-cloro-2-((4-*t*- butoxicarbonilpiperazin-1-il)metil)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(oxazol-2- ilaminometil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

1-((4-cloro-2-(morfolin-4-ilmetil)fenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1- ((4-bromo-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-fluoro-3-clorofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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1-((4-cloro-2-metoxicarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-metoxicarbonilfenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-aminocarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-carboxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans)*-1-((3-cianofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-metil-2-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-metil-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metoxicarbonilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3- nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-acetil-2-(aminocarbonil)fenoxi)metil)

carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-nitro-3-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((5-nitro-2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-amino-3-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5- nitro-2-aminofenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((2-aminofenoxi)metil)carbonil-2, 5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((3- metoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-metoxi-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-metoxi-2-acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((2-((2-hidroxietil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-((2-hidroxietoxi)carbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(2-hidroxietoxi)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-acetil-4,5- dimetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((5-metoxi-2-(metoxicarbonil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(*N'*- metilureido)amino)metil)piperazina;

(*trans*)-1-((4- metil-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((3-cloro-5-metoxifenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metoxi-5-nitrofenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((2-(hidroximetil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-metilfenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

1-((4-clorofenoxi)metil)carbonil-2- (2-azidoetil)-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ftalimido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(maleimido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((4-(bencilcarbonil) piperazin-1-il)metil)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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(*trans*)-1-((4-cloro-2-((4-((2,3, 4-trifluorofenil)aminocarbonil)piperazin-1-il)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-((2-fluorofenil)aminocarbonil)piperazin-1-il)metil) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(2,6-difluorofenil)ureido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(etenilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ciclopropilcarbonilamino)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ciclopentilcarbonilamino)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((furan-2-il)carbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(fenilcarbonilamino)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-((*N'*-(3-metoxifenil)ureido)feno-

xi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(metoxicarbonilmetilcarbonil)-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(2-metoxicarboniletil)carbonil-*N'*-(metil)glicinamido)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-metilbencil)aminocarbonil- *N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-trifluorometil-4-fluorofenil)carbonil-*N'*-(metil)glicinamido) fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(4-metilbencil)aminocarbonil-*N'*-(metil)glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(3-clorofenil)carbonil-*N'*-(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-(4-fluorobencil)aminocarbonil-*N'*-(metil)glicinamido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2-iodofenilcar-

bonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,3-difluorofenilcarbonil)glicinamido)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-((4-fenoxifenil)aminocarbonil)glicinamido)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2,4-diflurofenilcarbonil)glicinamido)fenoxi)metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((2-iodofenilcarbonil)aminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((etoxicarbonilmetilcarbonil)aminometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(3-cloropropil)ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2-fluoro-6-trifluorometilfenil)ureidometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((3-fluorofenil)carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-

fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(2-(etoxicarbonil)etil)ureidometil)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((2,5-di(trifluorometil)fenil)carbonilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-(*N'*-(2-(fenil)ciclopropil)ureidometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

9. El compuesto de la reivindicación 7, en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8)alquilo y hidroxi(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8) alquilcarbonilamino,

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halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1- C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8) alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil) ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1- C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

10. El compuesto de la reivindicación 9 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-((4-cloro-3-nitrofenoxi) metil)carbonil-2,5-

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dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(hidroximetil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-2- (aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*S*,5*R*)-1-((4-bromo-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-1-((3-hidroxi-5-metilfenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2 *S*,5*R*)-1-((4-nitro-3-formilfenoxi)metil)carbonil-2,5-dimetil- 4-(4-fluorobencil)piperazina;

(2R)-1-((4-clorofenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

4-(4- fluorobencil)-1-((4-clorofenoxi)metil)car-bonil-2-(2-hidroxietil) piperazina;

(*trans*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2,5- dimetilpiperazina;

(*trans*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-1-((4-cloro-3,5- dimetoxifenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*,5*S*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil)carbonil-2-(2-hidroxietil)-5-metilpiperazina;

(2*R*,6*R*)-4-(4-fluorobencil)-1-((4-clorofenoxi)metil) carbonil-2,6-dımetilpiperazina;

(*trans*)-1-((4-cloro-2- metoxifenoxi)metil)carbonil-2,5-dimetıl-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(hıdroxımetıl)fenoxi)metil)carbonil-2-metıl-4- (4-fluorobencıl)piperazina;

(2*R*,5*S*)-1-((4-cloro-3- (hidroximetil)fenoxi)me-til)carbonil-2,5-dimetil-4-(4-fluorobencıl) piperazina;

(*trans*)-1-((4-cloro-2-(1-hidroxietil)fenoxi)metil) carbonil-2,5-dimetıl-4-(4-fluorobencıl)piperazina;

(*trans*)-1-((4-cloro-2-(aminometil)fenoxi)metil)carbonıl-2,5-dımetıl-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(ureidometil)fenoxi)metil)carbonıl-2,5-dımetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-aminofenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(acetilamino)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-4-(4-fluorobencıl)-1-((2-acetilamino-4-clorofenoxi)metil)carbonil-2,5-dimetilpiperazina;

(*trans*)-1-((4-cloro-2-(propilcarbonilamino)fenoxi)metil)carbonil-2,5-dımetıl-4-(4-fluorobencil)piperazına;

(*trans*)-1-((4-cloro-2-(metoximetilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-(metoxicarbonil)etilcarbonilamino)fenoxi)-metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(2-etoxicarbonil)etilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metilsulfonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(bromometilcarbonilamino)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)-1-((4-cloro-2-(glicinamido) fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((*N'*-metilglicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(alaninamido)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((aminocarbonil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(aminocarbonil)(metil)glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-etiluredio)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(etilcarbonilamino)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-amino-5-nitrofenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina, sal diclorhidrato;

(*trans*)-1-((4-cloro-2-(((etil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((dietil)amino)metil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((ciclopropil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(((dimetil)amino)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(((metil)amino)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-((amino)metil)fenoxi) metil)car-

bonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-metilpiperazin-1-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi)metil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(etilaminometil)fenoxi)metil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(metilamino)etil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(1-(metilsulfonil)(metil)aminoetil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*)-1-((4-cloro-2-((piperazin-1-il)metil) fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4-cloro-2-((piperazin-1-il)metil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4-*t*-butoxicarbonilpiperazin-1-il) metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(imidazol-1-ilmetil)fenoxi) metil)carbonil-2,5-dimetil-4-(4-

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fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(1-(imidazol-1-il)etil)fenoxi)metil)carbonil- 2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(triazol-1-ilmetilo)fenoxi)metil) carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(tetrazol-1-ilmetil)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((morfolin-4-il)metil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)-1-((4-cloro-2-aminocarbonilfenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

1-((4-cloro-2-formilfenoxi)metil)carbonil-2- metil-4-(4-fluorobencil)piperazina;

(2*R*,5*S*)-1-((4- cloro-2-formilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(2*R*)-1-((4-cloro-2-formilfenoxi)metil) carbonil-2-metil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(metilaminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((aminocarbonilmetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((2-aminoetil)aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-((4- aminocarbonilo fenilo opcionalmente sustituido)aminocarbonil)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(hidroxiamidino)fenoxi)metil) carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2- acetilfenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((2-(aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4- cloro-2-((*N'*-(triclorometilcarbonil) ureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-((4-cloro-2-(*N'*-(metoximetilcarbonil)glicinamido)fenoxi) metil)-carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-((4-cloro-2-(*N'*-(etoxicarbonyiaminocarbonil) glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina.

11. El compuesto de la reivindicación 9, en el que R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y en la posición 2 por aminocarbonilo, ureido, o

glicinamido; a saber, el compuesto seleccionado del grupo formado por los siguientes compuestos:

(2*R*,5*S*)-1-((4-cloro-2- (aminocarbonil)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(glicinamido)fenoxi) metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*)- 1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

(*trans*)-1-((4-cloro-2-(ureido)fenoxi)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(2*R*, 5*S*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2,5-dimetil-4- (4-fluorobencil)piperazina; y

(2*R*,5*S*)-1-((4-cloro-2-(glicinamido)fenoxi)metil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

12. El compuesto de la reivindicación 9 en el que el compuesto más preferido es:

(2*R*)-1-((4-cloro-2-(ureido)fenoxi)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina;

13. El compuesto de la reivindicación 3 en el que:

R^4 es

-N(R^7)-;

R^5 es

metileno;

R^6 es

-C(O)-; y

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo.

14. El compuesto de la reivindicación 13 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8) alquiltio(C1-C8)alquilo,

hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8) alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8) alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, hidroxi(C1-C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo;

R^3 es

fenilo que se sustituye opcionalmente por uno o más

sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8) alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8)alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8) alquenilcarbonilamino, (C3-C10)cicloalquil-carbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8) alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo,

mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ((C1-C8) alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre) amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi) carbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo,

(aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil) aminocarbonilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil) glicinamido, (aminocarbonil)((C1-C8) alquil)glicina-mido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente

sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre) (C1-C8)alquilo.

15. El compuesto de la reivindicación 14 en elque:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1- C8) alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo,

(fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8) alcoxi, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido) (c1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(c1- C8)alquilamino, (C1-C8)alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de

nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)al-

quil)aminocarbonilo, (hidroxi(C1-C8)al-quil)amino-carbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8) alquil)ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8) alquilcarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo . o naftilo opcionalmente

sustituido)carbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(c1-C8) alquilaminocarbonil)((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8) alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

16. El compuesto de la reivindicación 15 en elque:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8) alquilo y hidroxi(C1-C8) alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-

C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (3C-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8) alquilcarbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8)alquil-sulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8) alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido) aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8) alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil) ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1- C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteróatomos seleccionados del grupo de nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

17. El compuesto de la reivindicación 16 en el que

R^2 es 4-fluoro y R^3 es fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido.

18. El compuesto de la reivindicación 17 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-((4-clorofenilamino)metil) carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

1-((4-cloro-2-(aminocarbonil)fenilamino)metil)carbonil-2-metil-4-(4-fluorobencil) piperazina; y

1-((4-clorofenilamino)metil)carbonil-2-metil-4-(4-fluorobencil)piperazina.

19. El compuesto de la reivindicación 3 en el que:

R^4 es

$-C(R^8)_2-$;

R^5 es

metileno;

R^6 es

$-C(O)-$; y

cada R^8

se selecciona en forma independiente entre el grupo formado por hidrógeno, (C1- C8) alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8)

alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre) carbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1- C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, y di(C1-C8)alquilamino(C1- C8)alquilo.

20. El compuesto de la reivindicación 19 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquilamino(C1-C8) alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidr-

oxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8) alquiltio(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8) alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, azido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil) ureido(C1-C8)alquilo, hidroxi(C1- C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos

seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo;

R^3 es

fenilo que se sustituye opcionalmente por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, hidroxi(C1-C8)alquilo, (mono(C1-C8) alquilamino) (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno,

oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di (C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8) alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8) alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alcoxicarbonilamino(C1- C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alcoxicarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (heterociclilo de 3 a

15 miembros

que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)amino(C1-C8) alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8) alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo, (amino(C1-C8)alquil) aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, di(C1-C8) alquilaminocarbonil(C1-C8) alquilo, hidroxiamidino, ureido, mono(C1-C8) alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8) alquil)ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)urei-

do(C1-C8) alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-C8)alquilcarbonil)glicinamido, (aminocarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8) alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil) glicinamido, (fenilo o naftilo opcionalmente sustituido) carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)carbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilaminocarbonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (3-15membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

21. El compuesto de la reivindicación 20 en el que: R^{1a} es

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uno o más sustituyentes seleccionados entre el grupo formado por (C1-C8) alquilo, (C3-C10)cicloalquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, ciano(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, y (3- 15 membered heterociclilo que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidroxi, halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, ciano, amino(C1-C8)alcoxi, (C3-C10)ciclo-alquilamino(C1-C8) alquilo, hidroxi(C1-C8) alquilo, (mono(C1-C8)alquilamino)(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquil-amino, di(C1-C8) alquilamino, mono(fenilo o naftilo

opcionalmente sustituido)(C1-C8)alquilamino, (C1-C8) alquilcarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10) cicloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1- C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8) alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1- C8)alquil) amino(C1-C8)alquilo, (cicloalquil(C1-C8)alquil)amino (C1-C8)alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquil-carbonilamino(C1-C8)alquilo, (C1-C8) alquilsulfonilamino(C1-C8)alquilo, ((C1-C8)alquilsulfonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino(C1-C8)alquilo, ((fenilo o

naftilo opcionalmente sustituido) sulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (C1-C8)alquilcarbonilo, (hidroxi(C1-C8)alcoxi)carbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil)aminocarbonilo; (amino(C1-C8)alquil)aminocarbonilo, (hidroxi(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, mono(C1-C8)alquilureido, mono(fenilo o naftilo opcionalmente sustituido)ureido, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilureido, (mono(C1-C8)alquil)(mono(fenilo o naftilo opcionalmente sustituido))ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, di(C1-C8) alquilureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido) ureido(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, (halo(C1-C8)alquil)((C1-C8)alquil) ureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil) ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1-

C8)alquilcarbo-nil)glicinamido, (aminocarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonil(C1-C8)alquilcarbonil)((C1-C8)alquil) glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)al-quilcarbonil)glicinamido, (fenilo o naftilo opcionalmente sustituido)carbonilglicinamido, ((fenilo o naftilo opcionalmente sustituido)car-bonil)((C1-C8)alquil) glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilaminocarbonil) ((C1-C8)alquil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil)glicinamido, (mono(fenilo o naftilo opcionalmente sustituido) aminocarbonil)((C1-C8)alquil)glicinamido, alaninamido, heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno,oxígeno y azufre)(C1-C8)alquilo.

22.El compuesto de la reivindicación 21 en el que: R^{1a} es

uno o más sustituyentes seleccionados entre el grupo

formado por (C1-C8) alquilo y hidroxi(C1-C8)alquilo;

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, cloro o fluoro;

R^3 es

fenilo sustituido por uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C1-C8)alcoxi, formilo, nitro, (C3-C10)cicloalquilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilo, amino, (C1-C8)alquilcarbonilamino, halo(C1-C8)alquilcarbonilamino, (C1-C8) alcoxi(C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonil(C1-C8) alquilcarbonilamino, (C1-C8)alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, ((C1-C8) alquilsulfonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, (aminocarbonil(C1-C8)alquil) aminocarbonilo, (amino(C1-C8)alquil)aminocarbonilo, hidroxiamidino, ureido, (halo(C1-C8)alquilcarbonil)ureido, ureido(C1-C8)alquilo, glicinamido, mono(C1-C8)alquilglicinamido, aminocarbonilglicinamido, ((C1-C8)alcoxi(C1- C8)alquilcarbonil)glicinamido,

(aminocarbonil)((C1-C8)alquil)glicinamido, ((C1-C8)alcoxicarbonilamino(C1-C8)alquilcarbonil)glicinamido, alaninamido, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo.

23. El compuesto de la reivindicación 22 en el que:

R^2 es

4- fluoro;

R^3 es

fenilo sustituido en la posición 4 con cloro y opcionalmente sustituido en la posición 2 por aminocarbonilo, ureido, o glicinamido; y

un R^8 es

hidrógeno y el otro R^8 es seleccionado del grupo formado por amino, (C1-C8) alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10) cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C1-C8) alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido) carbonilamino, (C1-C8)alcoxicarbonil(C1-C8)alquilcarbonilamino, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8) alquilo, (C1-C8)alcoxicarbonilamino(C1-C8)alquilo,

(heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre) carbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, y amino(C1-C8)alquilo.

24. El compuesto de la reivindicación 23 seleccionado del grupo formado por los siguientes compuestos:

(*trans*)-1-(2-(4-clorofenil)-3- (metilsulfonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(acetilamino) propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(metilsulfonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(acetilamino)etil)carbonil-2,5-dimetil-4-(4- fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(amino)etil)carbonil-2,5-

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dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(ureido)etil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-amino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*t*-butoxicarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((etoxicarbonilmetilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-*iso*-propilureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(*N'*-(2-cloroetil)ureido)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2-nitrofenil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((4-metoxifenilmetil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

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(*trans*)-1-(2-(4-clorofenil)-2-((2,4-dinitrofenil)sulfonilamino)etil)carbonil-2,5- dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-(ciclopropilcarbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-2-((2-ciclopropiletil)carbonilamino)etil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-((2-metilpropil)carbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(cicloppentilcarbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(*t*-butil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil) piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(etil)ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina;

(*trans*)-1-(2-(4-clorofenil)-3-(*N'*-(3-choropropil) ureido)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina; y

(*trans*)-1-(2-(4-clorofenil)-3-((morfolin-4-

il)carbonilamino)propil)carbonil-2,5-dimetil-4-(4-fluorobencil)piperazina.

25. El compuesto de la reivindicación 1 en el que:

R^3 es

un sistema de anillo heterocíclico sustituido por uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno, hidroxi, halo, (C1-C8) alquilo, (C1-C8)alquilsulfonilo, (fenilo o naftilo opcionalmente sustituido) sulfonilo, (C1-C8)alcoxi, hidroxi(C1-C8)alcoxi, halo(C1-C8)alquilo, formilo, nitro, ciano, halo(C1-C8) alcoxi, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8)alquilamino, mono(fenilo o naftilo opcionalmente sustituido)amino, mono(fenilo o naftilo opcionalmente sustituido) (C1-C8)alquilamino, (C1-C8)alquilcarbonilamino, (C1-C8)alcoxicarbonilamino, (C2-C8)alquenilcarbonilamino, (C3-C10)ci-cloalquilcarbonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, halo(C1-C8) alquilcarbonilamino, (C1-C8)alcoxi(C1-C8)alquilcarbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, ((C1-C8)alcoxicarbonil)((C1-

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C8)alquil)amino, (C1-C8) alquilsulfonilamino, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)carbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil)amino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, carboxi, (C1-C8)alcoxicarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxicarbonilo, (C1-C8) alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)carbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, aminocarbonilo, mono(C1-C8)alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo, di(C1-C8)alquilaminocarbonil(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)aminocarbonil(C1-C8)alquilo, guanidino, ureido, mono(C1- C8) alquilureido, ureido(C1-C8)alquilo, mono(C1-C8)alquilureido(C1-C8)alquilo, y glicinamido.

26. El compuesto de la reivindicación 25 en el que:

R^4 es

-O-, - N(R^7)- o -C(R^8)-;

R^5 es

una cadena (C1-C8) alquileno;

R^7 es

seleccionado del grupo formado por hidrógeno, (C1-C8)alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8) alquilcarbonilo, (C1-C8)alquilcarbonil(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil(C1-C8)alquilo, aminocarbonilo, mono(C1-C8) alquilaminocarbonilo, di(C1-C8)alquilaminocarbonilo, y (C1-C8) alcoxicarbonilo; y

cada R^8 es

seleccionado entre el grupo formado por hidrógeno, (C1-C8) alquilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilo, hidroxi, (C1-C8)alcoxi, hidroxi(C1-C8) alquilo, (C1-C8)alcoxi(C1-C8)alquilo, amino, mono(C1-C8)alquilamino, di(C1-C8) alquilamino, (C1-C8)alquilcarbonilamino, (C3-C10)cicloalquilcarbonilamino, (C3-C10)cicloalquil(C1-C8) alquilcarbonilamino, (C1-C8)alcoxicarbonilamino,

(C1-C8)alquilsulfonilamino, (fenilo o naftilo opcionalmente sustituido)carbonilamino, (C1-C8) alcoxicarbonil(C1-C8)alquilcarbonilamino, ((C1-C8)alquilcarbonil)((C1-C8) alquil)amino, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino, ((fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonil)((C1-C8)alquil)amino, (C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C3-C10)cicloalquilcarbonilamino(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alquilcarbonilamino(C1-C8)alquilo, (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)carbonilamino(C1-C8)alquilo, ((fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilcarbonil)((C1-C8) alquil)amino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido) sulfonilamino, (C1-C8)alquilsulfonilamino(C1-C8)alquilo, ureido, mono(C1-C8) alquilureido, monohalo(C1-C8)alquilureido, di(C1-C8)alquilureido, ureido(C1- C8)alquilo, mono(C1-

C8)alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8) alquilo, monohalo(C1-C8)alquilureido(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, carboxi(C1-C8) alquilo, (C1-C8)alcoxicarbonil(C1-C8)alquilo, aminocarbonil(C1-C8)alquilo, mono(C1-C8)alquilaminocarbonil(C1-C8)alquilo,y di(C1-C8) alquilaminocarbonil(C1-C8)alquilo.

27. El compuesto de la reivindicación 26 en el que:

R^4 es -O-;

R^5 es metileno; y

R^6 es -C(O)-.

28. El compuesto de la reivindicación 26 en el que:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por halo, (C1-C8)alquilo, (C3-C10) cicloalquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, halo(C1-C8)alquilo, hidroxi(C1-C8) alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8)alquilcarbonilamino(C1-C8)alquilo, (C1-C8) alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8) alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8)alquilo,

hidroxi(C1-C8) alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8)alquilamino(C1-C8) alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, azido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, ((C1-C8)alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, hidroxi(C1- C8) alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8) alquilcarbonil(C1-C8)alquilo, (C1-C8)alcoxicarbonilo, (C1-C8) alcoxicarbonil(C1-C8)alquilo, y (heterociclilo de 3 a 15 miembros que consiste de átomos de carbono y entre uno y cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre)(C1-C8)alquilo; y

R^2 es

uno o más sustituyentes seleccionados entre el grupo formado por hidrógeno y halo.

29. El compuesto de la reivindicación 28 R^3 seleccionado del grupo formado por azepinilo, acridinilo,

bencimidazolilo, benzotiazolilo, benzoxazolilo, benzopiranilo, benzopiranonilo, benzofuranilo, benzofuranonilo, benzotienilo, carbazolilo, cinnolinilo, decahidroisoquinolilo, dioxolanilo, furilo, isotiazolilo, quinuclidinilo, imidazolilo, imidazolinilo, imidazolidinilo, isotiazolidinilo, indolilo, isoindolilo, indolinilo, isoindolinilo, indanilo, indolizinilo, isoxazolilo, isoxazolidinilo, morfolinilo, naftiridinilo, oxadiazolilo, octahidroindolilo, octahidroisoindolilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxoazepinilo, oxazolilo, oxazolidinilo, piperazinilo, 4- piperidonilo, fenazinilo, fenotiazinilo, fenoxazinilo, ftalazinilo, pteridinilo, purinilo, pirrolilo, pirazolilo, pirazolidinilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, quinazolinilo, quinoxalinilo, quinolinilo, quinuclidinilo, isoquinolinilo, tiazolilo, tiazolidinilo, tiadiazolilo, triazolilo, tetrazolilo, tetrahidrofurilo, tetrahidropiranilo, tienilo, tiamorfolinilo, tiamorfolinilo sulfóxido, y tiamorfolinilsulfona.

30. El compuesto de la reivindicación 29 en el que R^3 es benzopiranilo, benzopiranonilo, benzfuranilo, benzofuranonilo, quinolinilo, indolilo, indolinilo, oxazolilo, imidazolilo, o benzotienilo.

31. El compuesto de la reivindicación 30, a saber: (*trans*)-1-((benzo[b]piran-2-on-7- iloxi)metil)carbonil-2,5-

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dimetil-4-(4-fluorobencil)piperazina.

32. Los compuestos

(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpiperazin-1-il]-3-oXopropenil]- fenil)-urea,

N-(5-Cloro-2-[(E)-3-[(R)-4-(4-fluorobencil)-2-metilpiperazin-1-il]-3- oxopropenil] fenil)-metansulfonamida,

(5-Cloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobencil)-2,5-dimetilpiperazin-1-il]-3-oxopropenil]-fenil)-urea,

N-(5-Cloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobencil)-2, 5-dimetilpiperazin-1-il]-3-oxopropenil]-fenil)-metansulfonamida,

metiléster de ácido (5-Cloro-2- {(E)-3-[4-(4-fluorobencil)-2-metil-piperazin-1-il]-3-oxo-propenil}-fenil)-acético,

ácido 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxo-propenil}- benzoico,

(5-cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxo-propenil}-4-metoxi-fenil)-urea,

(5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oxopropenil}-4-trifluorometoxi-fenil)-urea,

metiléster de ácido 5-Cloro-2-{(E)-3-[(R)-4-(4-fluoro-bencil)-2-metil-piperazin-1-il]-3-oXo-propenil}-4-metoxi-benzoico

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-

piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-propiónico,

ácido (5-Cloro-2-{2-[4-(3,4-difluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[4-(4-cloro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Bromo-2-{2-[(2R)-2-etil-4-(4-fluoro-bencil)-piperazin-1-il]-2-oxo-etoxi}-fenil)- acético,

ácido (5-Cloro-2-{2-[4- (4-cloro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acético,

ácido (5-Cloro-2-{2-[4-(3, 4-difluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acé-tico,

ácido 3-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxv}-fenil)-acrílico,

N-[(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-acetil]-

metansulfonamida,

N-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dımetıl-pıperazın-1-il]-2-oxo-etoxi}-benzoil)-metansulfonamıda,

N- [(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-ıl]-2-oxo-etoxı}-fenil)-acetil]-C,C,C-trifluoro-metansulfonamida,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxı}-fenıl)-oxo-acético,

ácıdo (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)- acético,

ácido 2-(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetıl-pıperazın-1-ıll-2-oxo-etoxi}-fenoxi)-2-metıl- propıónico,

ácido (5-Clóro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dımetil-piperazin-1-il]-2-oxo-etoxi}-fenoxi)-difluoro-acético

(5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxı}-fenıl)-metansulfonamida

N-[5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazınıl]-2-oxoetoxı]fenil-trıfluorometansulfonamida,

5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metıl]-2,5-dimetilpiperazınıl]-2-oxoetoxi]-bencensulfonamida.

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ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Bromo-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-metansulfónico,

ácido (5- Bromo -2-{2-[4-(4-fluoro-bencil)-(2R)-2-metil-piperazin-1-il]-2-oxo-etoxi}-fenil)- metansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-fenil)-etansulfónico,

ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R,5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfónico,

monoetiléster de ácido (5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R, 5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil) fosfónico,

ácido 5-Cloro-2-{2-[4-(4-fluoro-bencil)-(2R5S)-2,5-dimetil-piperazin-1-il]-2-oxo-etoxi}-bencil)-fosfonamídico

metiléster de ácido 5-cloro-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico

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metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético;

metiléster de ácido 5-bromo-2-[2-[(2*R*)-4-[(4- fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metilbenzoico;

metiléster de ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]benzoico;

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-(trifluorometil)benzoico;

metiléster de ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-

[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]benzoico;

metiléster de ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxibenzoico

metiléster de ácido 5-bromo-2-[2-[(2*R*)-4-[(5-cloro-2-tienil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencenacético

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencensulfónico;

ácido 5-cloro-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencensulfónico;

ácido 5-cloro-4-(dimetilamino)-2-[2-[(2R,5S)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]bencenacético

ácido 5-bromo-2-[2-[(2*R*)-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]bencen acético;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxibenzoico

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ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-metil- benzoico

ácido 4,5-dicloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico.

ácido 5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-4-(trifluorometil) benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi] benzoico;

ácido 5-bromo-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxi-benzoico;

ácido 5-cloro-4-etoxi-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 4-amino-5-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi] benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-5-etil-4-[(4-fluorofenil)metil]-2-metilpiperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 5-cloro-2-[2-[(2*R*,5*S*)-2,5-dietil-4-[(4-fluorofenil)metil]piperazinil]-2-oxoetoxi]-4-metoxi benzoico;

ácido 4-cloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-

dimetilpiperazinil]-2-oxoetoxi] benzoico;

ácido 2-[2-[(2*R*,5*S*)-4-[(4-fluorofenil)metil]-2,5-dimetilpiperazinil]-2-oxoetoxi]-5-metil benzoico

en la producción de un medicamento para el tratamiento y la prevención de la endometrosis en seres humanos

33. Uso de una composición farmacéutica que comprende una cantidad eficaz en términos terapéuticos de un compuesto como el descripto en cualquiera de las reivindicaciones 1 a 32 en la confección de un envase de medicamento para el tratamiento y la prevención de endometrosis en humanos.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SCHERING AKTIENGESELLSCHAFT
Corporate Patents
D-13342 Berlin
ALLEMAGNE

Patente

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11.05.2006
Applicant's or agent's file reference 53189AWO	**IMPORTANT NOTIFICATION**

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/002036	23 02 2005	24.02.2004

Applicant
SCHERING AKTIENGESELLSCHAFT et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority	Authorized Officer
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 53189AWO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No PCT/EP2005/002036	International filing date *(day/month/year)* 23 02 2005	Priority date *(day/month/year)* 24 02.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/495 A61K31/00		
Applicant SCHERING AKTIENGESELLSCHAFT et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36
2. This REPORT consists of a total of 5 sheets, including this cover sheet
3. This report is also accompanied by ANNEXES, comprising:
   - a ☒ *sent to the applicant and to the International Bureau)* a total of 57 sheets, as follows:
     - ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70 16 and Section 607 of the Administrative Instructions)
     - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No I and the Supplemental Box
   - b ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions)

4. This report contains indications relating to the following items

☒	Box No I	Basis of the report
☐	Box No II	Priority
☐	Box No III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No IV	Lack of unity of invention
☒	Box No V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
☐	Box No VI	Certain documents cited
☐	Box No VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 23 12 2005	Date of completion of this report 11 05 2006
Name and mailing address of the international preliminary examining authority European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Tx 523656 epmu d Fax +49 89 2399 - 4465	Authorized officer Johnson, C Telephone No +49 89 2399-8287

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002036

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55 2(a) and/or 55.3(a))

2 With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 2, 4-10, 12-230	as originally filed
3, 3a, 11	filed with the demand

Claims, Numbers

1-33	filed with the demand

Drawings, Sheets

1-6	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*
   - ☐ any table(s) related to sequence listing *(specify)*:

4 ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70 2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*
   - ☐ any table(s) related to sequence listing *(specify)*.

* *If item 4 applies, some or all of these sheets may be marked "superseded "*

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No.	Claims	
Inventive step (IS)	Yes:	Claims	1-33
	No:	Claims	
Industrial applicability (IA)	Yes.	Claims	1-33
	No:	Claims	

2 Citations and explanations (Rule 70 7):

see separate sheet

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V. Reasoned statement

Reference is made to the following documents:
D1: EP-A-1 254 899
D2: WO2004/002960

Novelty
The claims concern the use of compounds of formula (Ia) in the production of a medicament for the treatment and prevention of endometriosis. D1 discloses compounds corresponding to present formula (Ia) as antiinflammatory agents, but does not mention their use in the treatment of endometriosis. The compounds of D2 differ from the presently used compounds i.a. because the piperazine ring is attached to a quinoline ring
Claims 1-33 fulfil the requirements of Article 33(2) PCT.

Inventive step
D1 discloses the use of compounds falling within the scope of present formula (Ia) as inhibitors of the chemokines, MIP-1alpha and RANTES, for the treatment of inflammatory disorders in humans.
D2 states that "abnormal production of chemokines, such as RANTES and MIP-1a have been implicated in a wide range of human acute and chronic inflammatory diseases, including rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, endometriosis and respiratory diseases, such as asthma and allergic disorders".
The technical problem appears to be the provision of an effective treatment of endometriosis.
Although D2 teaches that the chemokine RANTES (which is known to bind to the CCR1, CCR3 and CCR5 receptors) may be implicated in inflammatory diseases including endometriosis, the skilled man would not be aware of the fact that selective CCR1 receptor antagonists would be particularly useful in the treatment of endometriosis. In Figure 2 of the application it has been shown that CCR1 mRNA is very significantly upregulated in endometriotic lesions in comparison to normal endometriotic tissue. This knowledge was apparently not available to the skilled person at the priority date of the application. Thus it would not have been obvious for

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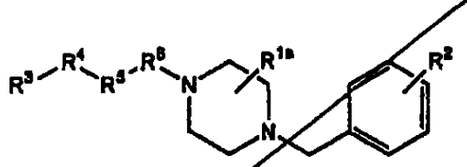
the skilled person to specifically use a selective CCR1 antagonist, rather than other RANTES competitors such as CCR5 antagonists, in the expectation that it would be particularly effective against endometriosis. The presently claimed subject matter, insofar as it does indeed have the alleged effect, may therefore be considered inventive.
Claims 1-33 fulfil the requirements of Article 33(3) PCT.

Industrial applicability
Claims 1-33 fulfil the requirements of Article 33(4) PCT.

(76) (Hoechst) describe piperazine derivatives as being useful as cardiotonic agents. European Published Patent Application 0 190 685 (G. D. Searle) describes piperazine derivatives which block the 5- lipoxygenase pathway of the arachidonic acid cascade, thereby being useful in the treatment of allergic and hypersensitivity reactions and inflammation. PCT Published Patent Application, WO 96/34864 (Schering Plough) discloses piperazine derivatives useful as neurokinin antagonists.
European Published Patent Application 1 254 899 (Schering AG) discloses the piperazine derivatives comprised in the present application for the treatment of an inflammatory disorder.
PCT patent application WO02/36581 (Schering AG) discloses also piperazine derivatives comprised in the present application for the diagnosing Alzheimer's disease.
All of the above references are incorporated herein in full by reference.
None of the above references describe the piperazine derivatives comprised in the present application for the treatment of endometriosis in human females, said piperazine derivatives being antagonists of Human Chemokine "C-C" receptor 1 (CCR1).

~~SUMMARY OF THE INVENTION~~

This invention is directed to the use of a compound of the following formula (Ia) or its pharmaceutically acceptable salt for the treatment and prevention of edometriosis in human wherein the treatment comprises administering to a human female in need of such treatment a therapeutically effective amount of said compound.
Accordingly, in one aspect, this invention provides compounds of the following formula (Ia):



(Ia)

wherein:
R^{1a} is
one or more substituents independently selected from the group consisting of oxo, halo, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, formyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl,

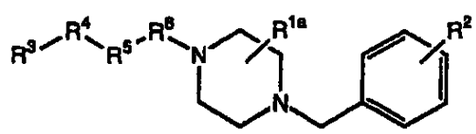
WO2004/002960A describes piperazine derivatives wherein the piperazine ring is attached to a quinoline ring. Said compounds are described to be selective antagonists for the Human Chemokine "C-C receptor 5" (CCR5). One of the diseses condition in which CCR5 antagonists have been implicated according to WO2004002960A is endometriosis.

The compounds of WO2004002960A however have a different structure and are active on a different receptor.

SUMMARY OF THE INVENTION

This invention is directed to the use of a compound of the following formula (Ia) or its pharmaceutically acceptable salt for the treatment and prevention of edometriosis in human wherein the treatment comprises administering to a human female in need of such treatment a therapeutically effective amount of said compound.

Accordingly, in one aspect, this invention provides compounds of the following formula (Ia):



(Ia)

wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, formyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl,

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(C=ONH-(C1-C8)alkyl, (C1-C8)alkyl-SO2-NH-(C1-C8)alkyl, (C2-C9)heteroaryl-(C1-C8)alkyl, H2N-(C=O)-,H2N- (C=O)- (Cl-C8) alkyl-;·

each R4 is independently selected from the group consisting of: H-, HO-, halo-, NC-, HO-(C=O-, H2N-, (C1-C8)alkyl-NH-, [(C1-C8)alkyl]2N-, (C1-C8)alkyl- optionally substituted with 1-3 fluorine atoms,(C1-C8) alkyl-O- wherein the alkyl group is optionally substituted with 1-3 fluorine atoms, HO-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C1-C8)alkyl-, H2N-(C1-C8)alkyl-, (C1-C8)alkyl NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C1-C8)alkyl-(C=O)-, (C1-C8)alkyl-(C=O)-(CC8) alkyl-, (C6-C10)aryl-, (C2-Cg) heteroaryl-, (C6-C10) aryloxy, H2N-(C=O), H2N-(C=O)-(CC8) alkyl, (C1-C8)alkyl-NH-(C=O)-, (C1-C8)alkyl-NH-(C=O)-(C1-C8)alkyl-, [(C1-C8)alkyl]2N (C=O)-, [(C1-C8)alkyl]2-N-(C=O)-(C1-C8)alkyl-, (C3-C8)cycloalkyl-, (C1-C8)alkyl-SO2-, NC-(C C8)alkyl-, (C1-C8) alkyl-(C=O)-NH-, H2N-(C=O)-NH-, H2N-(C=O)-NH-(C1-C8) alkyl-;

R5 is (C1-C8) alkyl-.

for the treatment and prevention of edometriosis.

Particularly favourable embodiments of the present invention are the following compounds as reported in ~~WO01/72728:~~ WO02/102787 :

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

The patent application WO2004/055031 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds of the formula I- WO2004/055031

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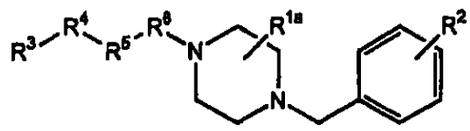
Claims:

1. Use of a compound of the following formula (Ia):



(Ia)

for the production of a medicament for the treatment and the prevention of edometriosis in human wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl) amino(C1-C8)alkyl, halo(C1-C8)alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2- C8)alkenyl, formyl, formyl(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2- C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, mercapto(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8) alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, azido(C1-C8)alkyl, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8) alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1- C8)alkyl, (C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or

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naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8) alkyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (C1- C8)alkylthio(C1-C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8) alkylsulfonyl(C1-C8)alkyl, (C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy, halo(C1-C8) alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy)(C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10) cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl)amino, ((C3- C10)cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, cyano(C1-C8)alkyl, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-

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C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8) alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1- C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8) alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkoxycarbonylamino(C1-C8) alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbony((C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C7-C8) alkylaminocarbonyl(C1-C8)alkyl, amidino, guanidino, ureido, mono(C1-C8) alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and

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sulfur and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^3 is

a carbocylic 3- to 15-membered ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8) alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1- C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, amino(C1-C8)alkylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino, alkylcarbonylamino, (C1-C8) alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-

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C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1- C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, di(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl,

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aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureidoalkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mona(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

or R^3 is

a 3-15 membered heterocyclic ring system consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen,

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oxygen and sulfur, substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8)alkoxy, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, amino, mono(C1- C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl(C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, monoalkylamino(C1-C8)alkyl, di(C1- C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1- C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido;

R^4 is

-O-, $-N(R^7)-$, $-C(R^8)_2-$ or a bond;

R^5 is

an (C1-C8) alkylene chain or an (C1-C8) alkylidene chain, or, if R^4 is a bond, R^5 is an (C1-C8) alkylidene chain optionally substituted by (optionally substituted phenyl or naphthyl) or $-N(R^7)_2$;

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or R^4 and R^5 together are –HC=CH-

R^6 is

-C(O)-, -C(S)-, $-CH_2-$ or a bond;

each R^7

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkylcarbonyl, (C1-C8) alkylcarbonyl(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1- C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8)alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) aminoalkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl,

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mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl;

provided that when R^4 is $-N(R^7)-$, R^3 cannot be a heterocyclic ring system containing 4-8 members consisting of carbon atoms and only one nitrogen atom; and provided that when R^4 is $-C(R^8)_2$ or a bond, R^3 cannot be a bridged saturated heterocyclic ring system containing 4-6 members consisting of carbon atoms and two nitrogen atoms, and as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

2. Use according to calim 1 of a compound as described in Claim 1 wherein:

R^3 is

a 3- to 15- membered carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8) alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino,

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amino(C1-C8)alkylamino, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, amino, ((C3-C10)cycloalkyl(C1- C8)alkyl) amino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, di(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl,

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aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon

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atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

3. Use according to claim 1 of a compound as defined in Claim 2 wherein:

R^4 is

-O-, -N(R^7)- or -C(R^8)-;

R^5 is

an (C1-C8)alkylene chain;

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8) alkyl,

((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8)alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbony4(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl.

4. Use according to claim 1 of a compound as defined in Claim 3 wherein:

R^4 is

-O-;

R^5 is

methylene; and

R^6 is

-C(O)-.

5. Use according to claim1 of a compound as defined in Claim 4 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2- C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-

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C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalky(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-CS)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)

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sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy) carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl) ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

6. Use according to claim 1 of a compound as defined in Claim 5 selected from the group consisting of the following compounds:

(2*S*)-1-((4-chlorophenoxy)methyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine;

1-((phenoxy)methyl) carbonyl-2-ethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl) -1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(methoxymethyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-((acetylamino)methyl)piperazine;

1-((4-chlorophenoxy) methyl)carbonyl-2-(2-((4-fluorobenzyl)amino)ethyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((methyl)amino)ethyl)-4- (4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl- 2-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methyl-5-methylpiperazine;

4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(methoxycarbonyl)methylpiperazine;

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-3-((methoxy)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-(methoxy) ethyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxypropyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxybut-4-ynyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine ;

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1-((4-chlorophenoxy)methyl)carbonyl-3- (2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine;

(2*S*,5*R*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*S*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(2-methylthio)ethylpiperazine;

(2*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy)methylpiperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((2- hydroxyethyl)thio)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(*N'*-(ethoxycarbonylmethyl) ureido) methyl)piperazine;

(2*R*,5*S*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((amino)carbonyloxy)methyl-4-(4-fluorobenzyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-((acetyl)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-5-(1-hydroxybutyl)piperazine;

(2*R*,5 *S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((diethylamino)methyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((dimethylamino)methyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine;

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1- yl)methyl)piperazine;

(*cis*)-1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine;

1-((phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

1-((2-(acetylamino)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxypropyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut- 3-enyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-3-trifluoromethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-((4-(2,5-di(trifluoromethyl)phenylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

7. Use according to claim 1 of a compound as defined in Claim 5 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8) alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3- C10)cycloalkylcarbonylamino, (optionally

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substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally

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substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

8. Use according to claim 1 of a compound as defined in Claim 7 selected from the group consisting of the following compounds:

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine;

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

(2*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

4-(4- fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl)spiro[cyclopropane-1, 2'-piperazine];

1-((4-chlorophenoxy)methyl)carbonyl-2- hydroxymethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(2-(methoxy)ethyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2-methylpropyl)amino)ethyl) -4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5-methylpiperazine;

(2*R*)-1-((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

(2*S*)-1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(hydroxymethyl) piperazine;

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4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxyethyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(((methyl)ureido)methyl)piperazine;

(2*R*,3*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,3-dimethylpiperazine;

(*cis*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5-methylpiperazine;

(2 *R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5((hydroxy)methyl)piperazine;

(2*R*,5*R*) -4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-((methoxy)-methyl)piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine;

(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxyethyl)piperazine;

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyprop-3-enyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl) piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl)piperazine;

(3*S*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3,5-dimethylpiperazine;

1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((ethyl)(1-methylbutyl)aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2- aminophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (benzylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*iso*-propylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-nitrophenyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-methylphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (acetylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(phenylsulfonyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- ((methyl)(ethyl)amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (dimethylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(oxazol-2- ylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-(morpholin-4-ylmethyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1- ((4-bromo-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-methoxycarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methyl-2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-methyl-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-nitro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- nitro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-4,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl)piperazine;

(*trans*)-1-((4- methyl-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((3-chloro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2- (2-azidoethyl)-4-(4-fluorobenzyl)piperazine;

(*trans*)-1- ((4-chloro-2-(phthalimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (maleimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((4-(benzylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2,3, 4-trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2,6-difluorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(ethenylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(cyclopropylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(cyclopentylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4-chloro-2-((furan-2-yl)carbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(3-methoxyphenyl)ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(methoxycarbonylmethylcarbonyl)-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2- methoxycarbonylethyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl)aminocarbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-trifluoromethyl-4-fluorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4- methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-chlorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4- fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,3-difluorophenylcarbonyl) glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4- chloro-2-(*N'*-(2,4-difluorophenylcarbonyl)glycinamido)phenoxy)methyl) -carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((ethoxycarbonylmethylcarbonyl) aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(3-chloropropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'* -(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)-methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((3-fluorophenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(*N'*-(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*S*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4- chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

9. Use according to claim 1 of a compound as defined in Claim 7 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl and hydroxy(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)

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alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

10. Use according to claim 1 of a compound as defined in Claim 9 selected from the group consisting of the following compounds:

(*trans*)-1-((4-chloro-3-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*S*,5*R*)-1-((4-bromo-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((3-hydroxy-5-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2 *S*,5*R*)-1-((4-nitro-3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(2R)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl) piperazine;

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(*trans*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine;

(2*R*,6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,6-dimethylpiperazine;

(*trans*)-1-((4-chloro-2- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-hydroxyethyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino- 4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(2- (methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-(glycinamido) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-ethylureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-amino-5-nitrophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt;

(*trans*)-1-((4-chloro-2-(((ethyl)amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((diethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(((cyclopropyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (((dimethyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((methyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4-chloro-2-((4-methylpiperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (methylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(methylsulfonyl) (methyl)aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(imidazol-1-ylmethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(triazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(tetrazol-1-ylmethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((morpholin-4-yl)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1-((4- chloro-2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4- chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1- ((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2- aminoethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4- aminocarbonyloptionally substituted phenyl)aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxyamidino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(methoxymethylcarbonyl)glycinamido)phenoxy) methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonylaminocarbonyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine.

11. Use according to claim 1 of a compound as defined in Claim 9 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4-position with chloro and at the 2-position by aminocarbonyl, ureido, or glycinamido; namely, the compound selected from the group consisting of the following compounds:

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(2*R*, 5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; and

(2*R*,5*S*)-1-((4- chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine.

12. Use according to claim 1 of a compound as defined in Claim 9 wherein the most preferred compound is:

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

13. Use according to claim 1 of a compound as defined in Claim 3 wherein:

R^4 is

-N(R^7)-;

R^5 is

methylene;

R^6 is

-C(O)-; and

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl.

14. Use according to claim 1 of a compound as defined in Claim 13 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)

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alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8) alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1-C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1- C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8)alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)

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alkoxycarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy) carbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting

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of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) (C1-C8)alkyl.

15. Use according to claim 1 of a compound as defined in Claim 14 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1- C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8) alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl) (c1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(c1- C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl,

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(cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(c1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

16 Use according to claim 1 of a compound as defined in Claim 15 wherein:

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R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (3C-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8) alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

17. Use according to claim 1 of a compound as defined in Claim 16 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4- position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido.

18. Use according to claim 1 of a compound as defined in Claim 17 selected from the group consisting of the following compounds:

(*trans*)-1-((4-chlorophenylamino)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-(aminocarbonyl)phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; and

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl- 4-(4-fluorobenzyl)piperazine.

19. Use according to claim 1 of a compound as defined in Claim 3 wherein:

R^4 is

$-C(R^8)_2-$;

R^5 is

methylene;

R^6 is

-C(O)-; and

each R^8

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, and di(C1-C8)alkylamino(C1- C8)alkyl.

20. Use according to claim 1 of a compound as defined in Claim 19 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl,

mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl,

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(cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8) alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl) aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, di(C1-C8) alkylaminocarbonyl(C1-C8) alkyl, hydroxyamidino, ureido, mono(C1-C8) alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five

heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

21. Use according to claim 1 of a compound as defined in Claim 20 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8) alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl,

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(cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl; (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

22 Use according to claim 1 of a compound as defined in Claim 21 wherein:

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R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8) alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1- C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

23. Use according to claim 1 of a compound as defined in Claim 22 wherein:

R^2 is

4- fluoro;

R^3 is

phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido; and

one R^8 is

hydrogen and the other R^8 is selected from the group consisting of amino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-

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C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, and amino(C1-C8)alkyl.

24. Use according to claim 1 of a compound as defined in Claim 23 selected from the group consisting of the following compounds:

(*trans*)-1-(2-(4-chlorophenyl)-3- (methylsulfonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(methylsulfonylamino)ethyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(acetylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- (amino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(ureido)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-3-(ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-3-(*t*-butoxycarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((ethoxycarbonylmethylcarbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'-iso*-propylureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

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(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'*-(2-chloroethyl)ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((2-nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((2,4-dinitrophenyl)sulfonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)- 2-((2-cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- ((2-methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (*t*-butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (ethyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl) ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

25. Use of a compound as described in Claim 1 wherein:

R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8) alkyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl) sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8) alkoxy, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino,

mono(optionally substituted phenyl or naphthyl) (C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1-C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido.

26. Use according to claim 1 of a compound as defined in Claim 25 wherein:

R^4 is

-O-, - N(R^7)- or -C(R^8)-;

R^5 is

an (C1-C8) alkylene chain;

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl; and

each R^8 is

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independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl.

27. Use according to claim 1 of a compound as defined in Claim 26 wherein:

R^4

is -O-;

R^5

is methylene; and

R^6

is -C(O)-.

28. Use according to claim 1 of a compound as defined in Claim 26 wherein:

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R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl; and

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo.

29. Use according to claim 1 of a compound as defined in Claim 28 wherein R^3 is selected from the group consisting of azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperazinyl, 4- piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl,

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thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone.

30. Use according to claim 1 of a compound as defined in Claim 29 wherein R^3 is benzopyranyl, benzopyranonyl, benzfuranyl, benzofuranonyl, quinolinyl, indolyl, indolinyl, oxazolyl, imidazolyl, or benzothienyl.

31. Use according to claim 1 of a compound as defined in Claim 30, namely, (*trans*)-1-((benzo[b]pyran-2-on-7- yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

32. Use according to claim 1 of any one of the following compounds:

(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oXopropenyl]- phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oxopropenyl] phenyl)-methanesulfonamide,

(5-Chloro-2-[(E)-3-[(2R, 5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-methanesulfonamide,

(5-Chloro-2- {(E)-3-[4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-phenyl)-acetic acid methyl ester,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-benzoic acid,

(5-chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-urea,

(5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxopropenyl}-4-trifluoromethoxy-phenyl)-urea,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oXo-propenyl}-4-methoxy-benzoic acid methyl ester

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-propionic acid,

(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4- (4-chloro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(3, 4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acrelic acid,

N-[(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-methanesulfonamide,

N- (5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzoyl)-methanesulfonamide,

N- [(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-C,C,C-trifluoro-methanesulfonamide,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-oxo-acetic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-acetic acid,

2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yll-2-oxo-ethoxy}-phenoxy)-2-methyl-propionic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-difluoro-acetic acid

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide

N-[5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]phenyl-trifluoromethanesulfonamide,

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]- benzenesulfonamide.

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

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(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl) phosphonic acid monoethyl ester,

5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R5S)-2,5-dimethYl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonamidic acid

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester;

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid methyl ester;

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid methyl ester;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

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5-bromo-2-[2-[(2*R*)-4-[(5-chloro-2-thienyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-4-(dimethylamino)-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-4-ethoxy-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

4-amino-5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzoic acid;

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5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

4-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-5-methylbenzoic acid.

33. Use of a pharmaceutical composition comprising a therapeutically effective amount of a compound as described in any one of the claims 1 to 32 for the production of a package of a medicament for the treatment and the prevention of edometriosis in human.

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

De la OFICINA INTERNACIONAL 1127

PCT

Notificación de registro de una modificación

(regla PCT 92bis 1 e
Instrucciones Administrativas , sección 422)

A

SCHERING AKTIENGESELLSCHAFT
Müllerstrasse 178
13353 Berlin
ALEMANIA

Fecha de envio *(día/mes/año)* *14 de agosto d 2006 (14 08 2006)*	
Referencia del solicitante o del agente *53189AWO*	**NOTIFICACIÓN IMPORTANTE**
Solicitud Internacional Nº *PCT/EP 2005/002036*	Fecha de presentacion *(día/mes/año)* *23 de febrero de 2005 (23 02 2005)*

1 Las siguientes indicaciones aparecen en los registros concernientes a
☒ el solicitante ☒ el inventor ☐ el agente ☐ el representante comun

Nombre y direccion	País de Nacionalidad	País de Residencia
HORUK, Richard *3410 Silver Springs Court* *Lafayette, CA 94549 California 94549* *Estados Unidos de América*	US	US
	Teléfono Nº	
	Facsimil Nº	
	Telex Nº	

2 La Oficina Internacional notifica por este medio al solicitante que se registró la siguiente modificación, concerniente a
☒ la persona ☐ el nombre ☐ la dirección ☐ la nacionalidad ☐ la residencia

Nombre y direccion	País de Nacionalidad	País de Residencia
HORUK, Richard *3410 Silver Springs Court* *Lafayette, CA 94549 California 94549* *Estados Unidos de América*	US	US
	Teléfono Nº	
	Facsimil Nº	
	Telex Nº	

3 Otras observaciones, si son necesarias
CAMBIO DE CATEGORIA la persona identificada en el campo 2 es ahora registrada como solicitante en los Estados Unidos de America solo e inventor para todos los estados designados

4 Se envia una copia de esta notificacion a

☒ la Oficina receptora ☐ las Oficinas concernientes designadas
☒ el Organismo de Busqueda Internacional ☒ las Oficinas concernientes seleccionadas
☐ el Organismo del Examen Preliminar Internacional ☐ otros

La Oficina Internacional de WIPO 34, chemin des Colombettes 1211 Geneva 20, Suiza Facsimil Nº (41-22) 338 82 70	Funcionario autorizado *Kirchner Maria* Facsimil Nº *(41-22) 338 89 70* Telefono Nº *(41-22) 338 80 56*

PCT/EP2005/002036

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To

SCHERING AKTIENGESELLSCHAFT
Müllerstrasse 178
13353 Berlin
ALLEMAGNE

Date of mailing *(day/month/year)* 14 August 2006 (14.08.2006)	
Applicant's or agent's file reference 53189Awo	IMPORTANT NOTIFICATION
International application No PCT/EP2005/002036	International filing date *(day/month/year)* 23 February 2005 (23.02.2005)

1 The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
HORUK, Richard 3410 Silver Springs Court Lafayette, CA 94549, California CA 94549 United States of America	US	US
	Telephone No.	
	Facsimile No	
	Teleprinter No.	

2 The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
HORUK, Richard 3410 Silver Springs Court Lafayette, CA 94549, California CA 94549 United States of America	US	US
	Telephone No	
	Facsimile No	
	Teleprinter No	

3 Further observations if necessary:
CHANGE OF STATUS. The person identified in Box 2 is now recorded as applicant for the United States of America only and inventor for all designated States.

4 A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No +41 22 338 82 70	Authorized officer Kirchner Maria Facsimile No +41 22 338 89 70 Telephone No. +41 22 338 80 56

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Europäisches Patentamt
Generaldirektion 2

D – 80298 München

Schering AG
Corporate Patents
Müllerstr 178
Berlin - Germany

E: alberto bartucco@schering de

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Your Ref	Your letter dated	Our Ref. (please indicate when replying)	Date
PCT/EP2005/002036		53189AWO	2005-12-23

Int. patent application PCT/EP2005/002036 in the name of Schering AG
Int. filing date: 23/02/2005
Title: PIPERAZINE DERIVATIVES FOR THE TREATMENT OF ENDOMETRIOSIS

In addition to the PCT Demand:

To the EPO in its Function as IPEA, amendments and arguments under art. 34 PCT

The applicant refers to the WOISA according to rule 43bis.1 date 17.05.05 (Authorized Officer: Johnson, C)

The applicant is submitting a new page 3, 3a and 11 of the description and a new set of claims, replacing page 3, and 11 of the description and the claims as originally filed.

1. The newly filed claims

The newly filed claims 2-32 were amended to meet the Authorized Officer's clarity objection and particularly the following wording was inserted:

"2. Use according to claim 1 of a compound as ~~described~~ defined in ~~of~~ Claim 1 wherein: ..."

Furthermore, claim 33 was also amended and reads now as follows:

"33. Use of a pharmaceutical composition ~~useful in treating endometriosis in a human female in need of such treatment, which composition comprises~~ comprising a therapeutically effective amount of a compound ~~according to claim 1~~ as described in any one of the claims 1 to 32 for the production of a package of a medicament for the treatment and the prevention of edometriosis in human."

Support for the amendment is found in the description page 214, line 4 where an example of a package is described.

The correction of page 11 of the description refers to a clerical error. WO01/72728 should have been WO02/102787 which is the document where the cited particularly favourable compounds are reported. Said compounds according to the invention can be used for the manufacture of a medicament for the treatment of endometriosis.

2. The piperazine derivatives of document D1 as selective CCR1 antagonists, and the new use according to present application in relation to the cited document D2.

The applicant positively acknowledge the opinion of the Authorized Officer stating the novelty of the subject matter according to the present application over D1 and D2.

EP1254899A (D1) describes piperazine derivatives being antagonists of Human Chemokine "C-C receptor 1" (CCR1), for the treatment of an inflammatory disorder. The compounds described in D1 compete with the chemokines MIP-1 and RANTES on the CCR-1 receptor inhibiting the activity of said chemokine. D1 was already cited in the present application.

According to the data supporting the present invention, infiltrating immune cells in the endometriotic-peritoneal lesions shows an up-regulated expression of CCR1 receptor. Said immune cells, like for example macrophages and T cells, regulate the inflammation process. Immune cells having such an up-regulated expression of the CCR1 receptor were not detected in the endomentrial tissue (Fig. 1 and 2).

The applicant kindly draw the attention of the Authorized Officer to the fact that the CCR1 antagonists described in the present invention have a direct and specific effect in modulating the inflammation process through the CCR-1 receptor of the immune cells in the endometriotic peritoneal lesion and can be used for the specific treatment of endometriosis.

WO2004002960A (D2) describes piperazine derivatives wherein the piperazine ring is attached to a quinoline ring. The compounds of D2 are described to be selective antagonists for the Human Chemokine "C-C receptor 5" (CCR5).

The Authorized Officer will immediately remark that the skilled person would never select compounds with a different structure and active on a different receptor to provide further treatments in endometriosis. D2 is clearly teaching away from the use of CCR-1 selective antagonists for the treatment of endometriosis.

To meet the requirements of Rule 5 (1)(ii) PCT, document D2 has been identified in the new page 3a of the description discussing the relevant background art disclosed therein. In so doing we took particular care in meeting the PCT requirements relative to the insertion of fresh matter.

It is believed that the features described in the newly filed claim 1, in the light of the above remarks, are new, original and cannot be derived from any other document cited in the international search report.

At the same time also new Claims 2 to 33 should be considered novel and meeting the requirements of Art. 33 (2), 33 (3) PCT.

The applicant believe the application is now in order for a positive International Preliminary Examination Report being issued. However, in case of further major objections, we are ready to discuss the matter of the present application directly with the Authorized Officer during an informal interview.

Yours sincerely,

SCHERING AKTIENGESELLSCHAFT

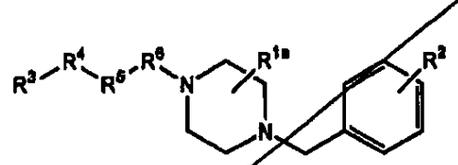
I.A.	p.pa.
A. Bertucco	Dr. T. Seuß
Corporate Patents	Corporate Patents

Encl.: new page 3, 3a and 11 of the description and a new set of the claims.

(Hoechst) describe piperazine derivatives as being useful as cardiotonic agents.
European Published Patent Application 0 190 685 (G D. Searle) describes piperazine derivatives which block the 5- lipoxygenase pathway of the arachidonic acid cascade, thereby being useful in the treatment of allergic and hypersensitivity reactions and inflammation. PCT Published Patent Application, WO 96/34864 (Schering Plough) discloses piperazine derivatives useful as neurokinin antagonists.
European Published Patent Application 1 254 899 (Schering AG) discloses the piperazine derivatives comprised in the present application for the treatment of an inflammatory disorder
PCT patent application WO02/36581 (Schering AG) discloses also piperazine derivatives comprised in the present application for the diagnosing Alzheimer's disease.
All of the above references are incorporated herein in full by reference.
None of the above references describe the piperazine derivatives comprised in the present application for the treatment of endometriosis in human females, said piperazine derivatives being antagonists of Human Chemokine "C-C" receptor 1 (CCR1).

~~SUMMARY OF THE INVENTION~~

This invention is directed to the use of a compound of the following formula (Ia) or its pharmaceutically acceptable salt for the treatment and prevention of edometriosis in human wherein the treatment comprises administering to a human female in need of such treatment a therapeutically effective amount of said compound.
Accordingly, in one aspect, this invention provides compounds of the following formula (Ia):



(Ia)

wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, formyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl,

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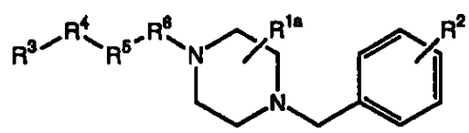
WO2004/002960A describes piperazine derivatives wherein the piperazine ring is attached to a quinoline ring. Said compounds are described to be selective antagonists for the Human Chemokine "C-C receptor 5" (CCR5). One of the diseses condition in which CCR5 antagonists have been implicated according to WO2004002960A is endometriosis.

The compounds of WO2004002960A however have a different structure and are active on a different receptor.

SUMMARY OF THE INVENTION

This invention is directed to the use of a compound of the following formula (Ia) or its pharmaceutically acceptable salt for the treatment and prevention of edometriosis in human wherein the treatment comprises administering to a human female in need of such treatment a therapeutically effective amount of said compound.

Accordingly, in one aspect, this invention provides compounds of the following formula (Ia):



(Ia)

wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, formyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl,

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(C=ONH-(C1-C8)alkyl, (C1-C8)alkyl-SO2-NH-(C1-C8)alkyl, (C2-C9)heteroaryl-(C1-C8)alkyl, H2N-(C=O)-,H2N- (C=O)- (Cl-C8) alkyl-;

each R4 is independently selected from the group consisting of: H-, HO-, halo-, NC-, HO-(C=O-, H2N-, (C1-C8)alkyl-NH-, [(C1-C8)alkyl]2N-, (C1-C8)alkyl- optionally substituted with 1-3 fluorine atoms,(C1-C8) alkyl-O- wherein the alkyl group is optionally substituted with 1-3 fluorine atoms, HO-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C1-C8)alkyl-, H2N-(C1-C8)alkyl-, (C1-C8)alkyl NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C1-C8)alkyl-(C=O)-, (C1-C8)alkyl-(C=O)-(CC8) alkyl-, (C6-C10)aryl-, (C2-Cg) heteroaryl-, (C6-C10) aryloxy, H2N-(C=O), H2N-(C=O)-(CC8) alkyl, (C1-C8)alkyl-NH-(C=O)-, (C1-C8)alkyl-NH-(C=O)-(C1-C8)alkyl-, [(C1-C8)alkyl]2N (C=O)-, [(C1-C8)alkyl]2-N-(C=O)-(C1-C8)alkyl-, (C3-C8)cycloalkyl-, (C1-C8)alkyl-SO2-, NC-(C C8)alkyl-, (C1-C8) alkyl-(C=O)-NH-, H2N-(C=O)-NH-, H2N-(C=O)-NH-(C1-C8) alkyl-;

R5 is (C1-C8) alkyl-.

for the treatment and prevention of edometriosis.

Particularly favourable embodiments of the present invention are the following compounds as reported in ~~WO01/72728:~~ WO02/102787 :

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

The patent application WO2004/055031 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds of the formula I- WO2004/055031

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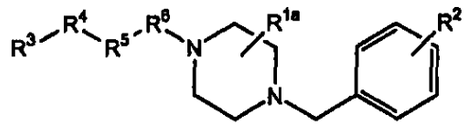
Claims:

1 Use of a compound of the following formula (Ia):



(Ia)

for the production of a medicament for the treatment and the prevention of edometriosis in human wherein.

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl) amino(C1-C8)alkyl, halo(C1-C8)alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2- C8)alkenyl, formyl, formyl(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2- C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, mercapto(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8) alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, azido(C1-C8)alkyl, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8) alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1- C8)alkyl, (C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or

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naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8) alkyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (C1- C8)alkylthio(C1-C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8) alkylsulfonyl(C1-C8)alkyl, (C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy, halo(C1-C8) alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy)(C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10) cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl)amino, ((C3- C10)cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, cyano(C1-C8)alkyl, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-

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C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8) alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1- C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8) alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkoxycarbonylamino(C1-C8) alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbony((C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C7-C8) alkylaminocarbonyl(C1-C8)alkyl, amidino, guanidino, ureido, mono(C1-C8) alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and

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sulfur and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^3 is

a carbocylic 3- to 15-membered ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8) alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1- C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, amino(C1-C8)alkylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino, alkylcarbonylamino, (C1-C8) alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-

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C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1- C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyt(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, di(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl,

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aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureidoalkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mona(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

or R^3 is

a 3-15 membered heterocyclic ring system consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen,

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oxygen and sulfur, substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8)alkoxy, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, amino, mono(C1- C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl(C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, monoalkylamino(C1-C8)alkyl, di(C1- C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1- C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido;

R^4 is

-O-, $-N(R^7)-$, $-C(R^8)_2-$ or a bond;

R^5 is

an (C1-C8) alkylene chain or an (C1-C8) alkylidene chain, or, if R^4 is a bond, R^5 is an (C1-C8) alkylidene chain optionally substituted by (optionally substituted phenyl or naphthyl) or $-N(R^7)_2$;

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or R^4 and R^5 together are –HC=CH-

R^6 is

-C(O)-, -C(S)-, $-CH_2-$ or a bond;

each R^7

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkylcarbonyl, (C1-C8) alkylcarbonyl(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1- C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8)alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) aminoalkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl,

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mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl;

provided that when R^4 is $-N(R^7)-$, R^3 cannot be a heterocyclic ring system containing 4-8 members consisting of carbon atoms and only one nitrogen atom; and provided that when R^4 is $-C(R^8)_2$ or a bond, R^3 cannot be a bridged saturated heterocyclic ring system containing 4-6 members consisting of carbon atoms and two nitrogen atoms, and as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof

2. Use according to calim 1 of a compound as described in Claim 1 wherein:

R^3 is

a 3- to 15- membered carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8) alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino,

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amino(C1-C8)alkylamino, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, amino, ((C3-C10)cycloalkyl(C1- C8)alkyl) amino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, di(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl,

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aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon

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atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

3 Use according to claim 1 of a compound as defined in Claim 2 wherein:

R^4 is

-O-, -N(R^7)- or -C(R^8)-;

R^5 is

an (C1-C8)alkylene chain;

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8) alkyl,

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((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8)alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbony4(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl.

4 Use according to claim 1 of a compound as defined in Claim 3 wherein:

R^4 is

-O-;

R^5 is

methylene; and

R^6 is

-C(O)-

5. Use according to claim1 of a compound as defined in Claim 4 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2- C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-

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C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalky(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-CS)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)

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sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy) carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl) ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

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6 Use according to claim 1 of a compound as defined in Claim 5 selected from the group consisting of the following compounds:

(2*S*)-1-((4-chlorophenoxy)methyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine;

1-((phenoxy)methyl) carbonyl-2-ethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl) -1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(methoxymethyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-((acetylamino)methyl)piperazine,

1-((4-chlorophenoxy) methyl)carbonyl-2-(2-((4-fluorobenzyl)amino)ethyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((methyl)amino)ethyl)-4- (4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl- 2-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methyl-5-methylpiperazine;

4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(methoxycarbonyl)methylpiperazine;

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-3-((methoxy)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-(methoxy) ethyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxypropyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxybut-4-ynyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine ;

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1-((4-chlorophenoxy)methyl)carbonyl-3- (2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine,

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine;

(2*S*,5*R*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*S*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine,

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(2-methylthio)ethylpiperazine,

(2*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy)methylpiperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((2- hydroxyethyl)thio)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(*N'*-(ethoxycarbonylmethyl) ureido) methyl)piperazine,

(2*R*,5*S*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((amino)carbonyloxy)methyl-4-(4-fluorobenzyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-((acetyl)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-5-(1-hydroxybutyl)piperazine;

(2*R*,5 *S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((diethylamino)methyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((dimethylamino)methyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine;

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1- yl)methyl)piperazine;

(*cis*)-1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine;

1-((phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

1-((2-(acetylamino)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxypropyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut- 3-enyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-3-trifluoromethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-((4-(2,5-di(trifluoromethyl)phenylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

7. Use according to claim 1 of a compound as defined in Claim 5 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8) alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3- C10)cycloalkylcarbonylamino, (optionally

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substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally

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substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

8 Use according to claim 1 of a compound as defined in Claim 7 selected from the group consisting of the following compounds:

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine;

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

(2*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

4-(4- fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl)spiro[cyclopropane-1, 2'-piperazine];

1-((4-chlorophenoxy)methyl)carbonyl-2- hydroxymethyl-4-(4-fluorobenzyl)piperazine,

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(2-(methoxy)ethyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2-methylpropyl)amino)ethyl) -4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine,

1-((4- chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5-methylpiperazine;

(2*R*)-1-((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

(2*S*)-1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(hydroxymethyl) piperazine;

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4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxyethyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(((methyl)ureido)methyl)piperazine;

(2*R*,3*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,3-dimethylpiperazine;

(*cis*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5-methylpiperazine;

(2 *R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5((hydroxy)methyl)piperazine,

(2*R*,5*R*) -4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-((methoxy)-methyl)piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine;

(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxyethyl)piperazine;

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyprop-3-enyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl) piperazine,

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl)piperazine;

(3*S*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3,5-dimethylpiperazine;

1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((ethyl)(1-methylbutyl)aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

1-((4-chloro-2- aminophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (benzylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*iso*-propylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-nitrophenyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-methylphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (acetylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(phenylsulfonyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

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(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- ((methyl)(ethyl)amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (dimethylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(oxazol-2- ylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-(morpholin-4-ylmethyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(trans)-1- ((4-bromo-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-methoxycarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans)*-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

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(*trans*)-1-((4-methyl-2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methyl-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-nitro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- nitro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-4,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl)piperazine;

(*trans*)-1-((4- methyl-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((3-chloro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2- (2-azidoethyl)-4-(4-fluorobenzyl)piperazine;

(*trans*)-1- ((4-chloro-2-(phthalimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (maleimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((4-(benzylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2,3, 4-trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((*N'*-(2,6-difluorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(ethenylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-(cyclopropylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(cyclopentylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4-chloro-2-((furan-2-yl)carbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(3-methoxyphenyl)ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(methoxycarbonylmethylcarbonyl)-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2- methoxycarbonylethyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl)aminocarbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-trifluoromethyl-4-fluorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4- methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-chlorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4- fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,3-difluorophenylcarbonyl) glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4- chloro-2-(*N'*-(2,4-difluorophenylcarbonyl)glycinamido)phenoxy)methyl) -carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((ethoxycarbonylmethylcarbonyl) aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(3-chloropropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'* -(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)-methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((3-fluorophenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(*N'*-(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*S*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4- chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

9. Use according to claim 1 of a compound as defined in Claim 7 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl and hydroxy(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)

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alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

10. Use according to claim 1 of a compound as defined in Claim 9 selected from the group consisting of the following compounds:

(*trans*)-1-((4-chloro-3-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*S*,5*R*)-1-((4-bromo-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((3-hydroxy-5-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2 *S*,5*R*)-1-((4-nitro-3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(2R)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine,

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl) piperazine;

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(*trans*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine;

(2*R*,6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,6-dimethylpiperazine;

(*trans*)-1-((4-chloro-2- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-hydroxyethyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2- (ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino- 4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(2- (methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-(glycinamido) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-ethylureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(*trans*)-1-((4-chloro-2-amino-5-nitrophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt;

(*trans*)-1-((4-chloro-2-(((ethyl)amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((diethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(((cyclopropyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (((dimethyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((methyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-((4-chloro-2-((4-methylpiperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (methylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(methylsulfonyl) (methyl)aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(imidazol-1-ylmethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(triazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(tetrazol-1-ylmethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((morpholin-4-yl)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1-((4- chloro-2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4- chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1- ((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2- aminoethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4- aminocarbonyloptionally substituted phenyl)aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxyamidino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(methoxymethylcarbonyl)glycinamido)phenoxy) methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonylaminocarbonyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine.

11. Use according to claim 1 of a compound as defined in Claim 9 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4-position with chloro and at the 2-position by aminocarbonyl, ureido, or glycinamido; namely, the compound selected from the group consisting of the following compounds:

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

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(2*R*, 5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; and

(2*R*,5*S*)-1-((4- chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine.

12. Use according to claim 1 of a compound as defined in Claim 9 wherein the most preferred compound is:

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

13. Use according to claim 1 of a compound as defined in Claim 3 wherein:

R^4 is

-N(R^7)-;

R^5 is

methylene;

R^8 is

-C(O)-; and

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl.

14 Use according to claim 1 of a compound as defined in Claim 13 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)

alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8) alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1-C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1- C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8)alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)

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alkoxycarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy) carbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting

of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) (C1-C8)alkyl

15. Use according to claim 1 of a compound as defined in Claim 14 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1- C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8) alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl) (c1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(c1- C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl,

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(cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(c1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

16. Use according to claim 1 of a compound as defined in Claim 15 wherein:

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R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (3C-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8) alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

17. Use according to claim 1 of a compound as defined in Claim 16 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4- position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido.

18. Use according to claim 1 of a compound as defined in Claim 17 selected from the group consisting of the following compounds:

(*trans*)-1-((4-chlorophenylamino)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-(aminocarbonyl)phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; and

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl- 4-(4-fluorobenzyl)piperazine.

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19. Use according to claim 1 of a compound as defined in Claim 3 wherein:

R^4 is

$-C(R^8)_2-$;

R^5 is

methylene,

R^6 is

-C(O)-, and

each R^8

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, and di(C1-C8)alkylamino(C1- C8)alkyl.

20 Use according to claim 1 of a compound as defined in Claim 19 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl,

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mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl,

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(cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8) alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl) aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, di(C1-C8) alkylaminocarbonyl(C1-C8) alkyl, hydroxyamidino, ureido, mono(C1-C8) alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five

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heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

21. Use according to claim 1 of a compound as defined in Claim 20 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8) alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl,

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(cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl; (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

22. Use according to claim 1 of a compound as defined in Claim 21 wherein:

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R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8) alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1- C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

23. Use according to claim 1 of a compound as defined in Claim 22 wherein:

R^2 is

4- fluoro,

R^3 is

phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido; and

one R^6 is

hydrogen and the other R^6 is selected from the group consisting of amino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-

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C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, and amino(C1-C8)alkyl.

24. Use according to claim 1 of a compound as defined in Claim 23 selected from the group consisting of the following compounds:

(*trans*)-1-(2-(4-chlorophenyl)-3- (methylsulfonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(methylsulfonylamino)ethyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(acetylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- (amino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(ureido)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-3-(ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-3-(*t*-butoxycarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((ethoxycarbonylmethylcarbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'-iso*-propylureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

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(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'*-(2-chloroethyl)ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((2-nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((2,4-dinitrophenyl)sulfonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)- 2-((2-cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- ((2-methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (*t*-butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (ethyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl) ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

25. Use of a compound as described in Claim 1 wherein:

R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8) alkyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl) sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8) alkoxy, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino,

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mono(optionally substituted phenyl or naphthyl) (C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1-C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido.

26. Use according to claim 1 of a compound as defined in Claim 25 wherein:

R^4 is

-O-, - N(R^7)- or -C(R^8)-;

R^5 is

an (C1-C8) alkylene chain;

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl; and

each R^8 is

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independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl.

27. Use according to claim 1 of a compound as defined in Claim 26 wherein:

R^4

is -O-;

R^5

is methylene; and

R^6

is -C(O)-.

28. Use according to claim 1 of a compound as defined in Claim 26 wherein.

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R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl; and

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo.

29. Use according to claim 1 of a compound as defined in Claim 28 wherein R^3 is selected from the group consisting of azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperazinyl, 4- piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl,

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thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone.

30. Use according to claim 1 of a compound as defined in Claim 29 wherein R^3 is benzopyranyl, benzopyranonyl, benzfuranyl, benzofuranonyl, quinolinyl, indolyl, indolinyl, oxazolyl, imidazolyl, or benzothienyl.

31. Use according to claim 1 of a compound as defined in Claim 30, namely, (*trans*)-1-((benzo[b]pyran-2-on-7- yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

32. Use according to claim 1 of any one of the following compounds:

(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oXopropenyl]- phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oxopropenyl] phenyl)-methanesulfonamide,

(5-Chloro-2-[(E)-3-[(2R, 5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-methanesulfonamide,

(5-Chloro-2- {(E)-3-[4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-phenyl)-acetic acid methyl ester,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-benzoic acid,

(5-chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-urea,

(5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxopropenyl}-4-trifluoromethoxy-phenyl)-urea,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oXo-propenyl}-4-methoxy-benzoic acid methyl ester

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-propionic acid,

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(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4- (4-chloro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(3, 4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acrelic acid,

N-[(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-methanesulfonamide,

N- (5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzoyl)-methanesulfonamide,

N- [(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-C,C,C-trifluoro-methanesulfonamide,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-oxo-acetic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-acetic acid,

2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yll-2-oxo-ethoxy}-phenoxy)-2-methyl-propionic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-difluoro-acetic acid

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide

N-[5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]phenyl-trifluoromethanesulfonamide,

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]- benzenesulfonamide.

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

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(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl) phosphonic acid monoethyl ester,

5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R5S)-2,5-dimethYl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonamidic acid

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester;

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid methyl ester;

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid methyl ester;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

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5-bromo-2-[2-[(2*R*)-4-[(5-chloro-2-thienyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-4-(dimethylamino)-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid,

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid.

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid,

5-chloro-4-ethoxy-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

4-amino-5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzoic acid;

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5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

4-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-5-methylbenzoic acid.

33. Use of a pharmaceutical composition comprising a therapeutically effective amount of a compound as described in any one of the claims 1 to 32 for the production of a package of a medicament for the treatment and the prevention of edometriosis in human.

TRATADO DE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

PCT

Informe de Búsqueda Internacional

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(Artículo PCT 18, así como reglas PCT 43 y 44)

Referencia del solicitante o del agente		
53189AWO	**PROCEDER** Ver notificación del envío del informe de búsqueda internacional (formulario PCT/ISA/220), así como, en tanto corresponda, el siguiente punto 5	
Referencia Internacional	Fecha de presentación Internacional	Fecha de prioridad (la más antigua) (día/mes/año)
PCT/EP 2005/002036	23 02 2005	24 02 2004
°Solicitante		
SCHERING AKTIENGESELLSCHAFT		

Este Informe de Búsqueda Internacional fue elaborado por el Organismo de Búsqueda Internacional y, de acuerdo con el artículo 18, es enviado al solicitante Se envía una copia a la Oficina Internacional

Este informe de búsqueda internacional comprende, en total, 5 hojas

☒ Además se adjunta una copia de cada uno de los antecedentes del estado de la técnica mencionados en este informe

1 **Fundamentos del Informe**

a Con respecto al idioma, la búsqueda internacional, en tanto no se indique otra cosa en este punto, fue llevada a cabo en el idioma en que se basa la solicitud internacional presentada

☐ La búsqueda internacional fue llevada a cabo basada sobre una traducción de la solicitud internacional presentada ante el organismo (regla 23 1 b))

b ☐ Con respecto a los **nucleótidos y/o aminoácidos** revelados en la solicitud internacional, ver campo Nº 1

2 ☒ **Determinadas reivindicaciones no eran investigables** (ver campo II)

3 ☐ **Escasa uniformidad de la invención** (ver campo III).

4 Con respecto **al título de la invención**,

☐ se aprueba el texto presentado por el solicitante

☒ el texto fue establecido por el organismo como sigue

DERIVADOS DE PIPERAZINA PARA EL TRATAMIENTO DE ENDOMETROSIS

5 Con respecto al **resumen**,

☒ se aprueba el texto presentado por el solicitante

☐ el texto fue establecido por el organismo de acuerdo con la regla 38 2 b) de la versión indicada en el campo III El solicitante puede presentar una posicion ante el organismo en el transcurso de un mes a partir de la fecha del envío de este Informe de Búsqueda Internacional

6 Con respecto a las **ilustraciones**

a Con el resumen se debe publicar la siguiente figura de Las **ilustraciones** figura Nº

☐ sugerida el solicitante

☐ seleccionada por el organismo, dado que el mismo solicitante no sugiere ninguna figura

☐ seleccionada por el organismo, dado que esta figura caracteriza mejor la invención

b ☐ con el resumen no se publica ninguna de las ilustraciones

1197

INFORME DE BÚSQUEDA INTERNACIONAL

Referencia Internacional
PCT/EP 2004/002036

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

IPC 7 A61K31/495

1190

Segun la clasificación internacional de patentes (IPK) o la clasificación internacional la IPK

B. ÁMBITOS INVESTIGADOS

Material mínimo investigado (Sistema de clasificacion y símbolos de clasificacion)

Publicaciones investigadas pero no pertenecientes al material mínimo investigado, en tanto pertenezcan al ámbito investigado

Banco electrónico de datos consultado durante la busqueda internacional (nombre del banco de datos y expresiones de busqueda eventualmente empleadas)

EPO-Internal, WPI Data

C ANTECEDENTES CONSIDERADOS RELEVANTES

Categoría*	Denominación de la publicación, así como, de ser requerido, indicacion de las piezas consideradas	Con referencia a reivindicación Nº
Y	*EP 1 254 899 A (SCHERING AKTIENGESELLSCHAFT)* *6 de noviembre de 2002 (2002 11 06)* *mencionado en la solicitud* *párrafo '0012!*	*1 – 32*
X	*reivindicación 33*	*33*
Y	*WO 20074/*002960 A (SCHERING AKTIENGESELLSCHAFT, DUNNING, LAURA, JAROCH STEPHAN, KOCHANNY)* *8 de enero de 2004 (2004 01 08)* *página 1, renglón 30 – página 2- renglón 1,* *reivindicaciones 20, 21*	*1 – 32*

☐ Se pueden escoger otras publicaciones en la continuacion del campo C

☒ Ver familia de patentes en el anexo

* Categorías particulares indicadas en publicaciones

"A" publicacion que define el estado general de la técnica pero no considerada como particularmente importante

"B" documento anterior pero publicado recién o despues de la de la fecha de presentación internacional

"L" publicacion adecuada para hacer aparecer como dudosa una reivindicación de prioridad, o mediante la cual debe ser considerada la fecha de divulgacion de otra publicacion mencionada en el informe de busqueda o que es indicada por otra razón particular (como realizada)

"O" publicación que se refiere a una revelacion oral, a una utilización, a una exposicion o a otras disposiciones

"P" publicacion realizada antes de la fecha de presentacion internacional pero luego de la fecha de prioridad reivindicada

"T" publicaciones posteriores a las difundidas en la fecha de presentación internacional o de la fecha de prioridad y que no colisionan con la solicitud, sino que solo están indicadas para mayor entendimiento del principio fundamental de la invención o de la teoría sobre la cual se basa

"X" publicación de particular importancia la invención reivindicada no puede ser considerada, solo como consecuencia de esta publicación, como novedosa o apoyarse en una actividad inventiva

"Y" publicación de particular importancia la invención reivindicada no puede ser considerada como apoyada en una actividad inventiva cuando puede ser relacionada con una o varias otras publicaciones de esta categoría y tal relacion es notoria para un especialista

"&" publicación que es miembro de la misma familia

Fecha de finalización de la busqueda internacional	Fecha de envío del Informe de Busqueda Internacional
17 de mayo de 2005	*23 05 2005*
Nombre y Código Postal de ISA European Patent Office – P B 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl Fax (+31-70) 340-3016	Funcionario Apoderado *Johnson, C*

1/92

INFORME DE BÚSQUEDA INTERNACIONAL

Referencia Internacional

PCT/EP 2005/002036

Campo II Observaciones porque determinadas reivindicaciones no eran investigables (continuación del ítem 2 de la hoja 1)

Este Informe de Búsqueda Internacional no fue realizado con respecto a algunas reivindicaciones, segun el artículo 17(2)(a), por las siguientes razones 1/91

1 ☐ Reivindicaciones Nº
a pesar de que las reivindicaciones se refieren a un procedimiento para el tratamiento del cuerpo humano/animal, la busqueda fue llevada a cabo y se basó sobre los efectos indicados del compuesto/composición

2 ☒ Reivindicaciones Nº *2 - 32*
porque se refieren a partes de la Solicitud Internacional que no cumplen con los requisitos prescriptos en una extension que no permite llevar a cabo una búsqueda internacional, especificamente

Ver INFORMACION ADICIONAL hoja PCT/ISA/210

3 ☐ Reivindicaciones Nº
porque son reivindicaciones dependientes y no están desarrolladas en acordanza con la segunda y la tercera frase de la regla 6 4(a)

Campo III: Observaciones por falta de uniformidad de la invención (continuación del ítem 3 de la hoja 1)

Este Organismo de Búsqueda Internacional encontro invenciones múltiples en esta solicitud internacional, a saber

1 ☐ Como todas las tasas adicionales fueron abonadas en término por el solicitante, este Informe de Busqueda Internacional cubre todas las reivindicaciones investigables

2 ☐ Como todas las reivindicaciones investigables pueden ser investigadas sin un esfuerzo que justifique una tasa adicional, este Organismo no solicita ningun pago o tasa adicional

3 ☐ Como solo algunas de las tasas adicionales fueron abonadas en término por el solicitante, este Informe de Busqueda Internacional cubre solo aquellas reivindicaciones para los cuales fueron abonadas las tasas, especificamente, las reivindicaciones Nº

4 ☐ Ninguna de las tasas adicionales requeridas fue abonada en término por el solicitante En consecuencia, este Informe de Busqueda Internacional está restringido a la invencion mencionada inicialmente en las reivindicaciones, la misma está cubierta por las reivindicaciones Nº

Observaciones sobre protestas

☐ Las tasas adicionales fueron acompañadas por la protesta del solicitante

☐ Las tasas adicionales no fueron acompañadas por ninguna protesta

1192

Continuación del campo II 2

Reivindicaciones Nº 2 – 32 (en parte)

La reivindicación 1, la reivindicación independiente central de la solicitud, cubre el uso de compuestos que responden a la fórmula (Ia) para la producción de un medicamento para el tratamiento y prevención de la endometrosis, es decir, no reivindica compuestos pero sí su uso medicinal La reivindicación 2 es dependiente de la reivindicación 1, pero se refiere a "el compuesto de la reivindicación 1" Existe así una contradicción entre las reivindicaciones, con lo que no se cumple con los requisitos del artículo PCT 6 No queda claro si el objeto cubierto por las reivindicaciones independientes es el compuesto en sí o su uso en la producción de un medicamento La descripción se refiere a 2 solicitudes de patente publicadas del presente solicitante e indica que revela los derivados de piperazina comprendidos en la presente solicitud, pero no describe su uso específico en la/el prevención/tratamiento de la endometrosis La presente búsqueda y examen se basó así solo en su uso, y los compuestos en sí no fueron investigados ni examinados

Se hace notar al solicitante el hecho de que las reivindicaciones relacionadas con la invención y con respecto a las cuales no se confeccionó un informe de búsqueda internacional no requieren ser sometidas a un examen preliminar internacional (regla PCT 66 1(e)) El solicitante es advertido de que la política del EPO, cuando actúa como Organismo de Examen Preliminar Internacional, es no proceder normalmente a un examen preliminar sobre objetos sobre los cuales no se realizó una búsqueda Este es el caso, independientemente de si las reivindicación fueron o no enmendadas siguiendo sugerencias del informe de búsqueda o durante cualquier procedimiento del capítulo II Se hace recordar al solicitante que si la solicitud procede en la fase regional antes que en el EPO, se lleva a cabo una búsqueda durante el examen ante el EPO (ver instrucción EPO C-VI, 8 5), en caso de superar los problemas surgidos de la declaración del artículo 17(2)

INFORME DE BÚSQUEDA INTERNACIONAL

Detalle de publicaciones que pertenecen a la misma familia de patentes

Referencia Internacional

PCT/EP 2005/002036

Documentos de Patente citados en el Informe de Busqueda			Fecha de la publicación	Miembros de la familia de patentes			Fecha de la publicación
EP	1254899	A	06 11 2002	US	6207665	B1	27 03 2001
				EP	1254899	A2	06 11 2002
				AT	232522	T	15 02.2003
				AU	735462	B2	12 07.2001
				AU	8625898	A	30 12 1998
				CA	2293382	A1	17 12.1998
				DE	69811363	D1	20 03 2003
				DE	69811363	T2	27 11 2003
				DK	988292	T3	22 04 2003
				EA	4038	B1	25 12 2003
				EE	9900565	A	15 06 2000
				EE	200200682	A	15 04.2003
				EE	200200683	A	15 04 2003
				EE	200200684	A	15 04 2003
				WO	9856771	A2	17 12 1998
				EP	0988292	A2	29 03 2000
				ES	2191320	T3	01 09 2003
				HU	0003929	A2	28 05 2001
				IL	132398	A	31 08 2004
				JP	2002503239	T	29 01 2002
				NO	996098	A	11.02 2000
				NO	20031373	A	11 02 2000
				PL	337758	A1	11 09 2000
				SK	171399	A3	12 09 2000
				TR	9903034	T2	21 06 2000
				US	2003158205	A1	21 08 2003
				US	2003139425	A1	24 07 2003
				US	6541476	B1	01 04 2003
				US	6534509	B1	18 03 2003
				US	6573266	B1	03 06 2003
				US	2002177598	A1	28 11 2002
wo	2004002960	A	08 01 2004	AU	2003247772	A1	19 01 2004
				BR	0312204	A	26 04 2006
				CA	2489560	A1	08 01 2004
				WO	2004002960	A1	08 01 2004
				US	2004072818	A1	15 04 2004

1193

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

1194

Applicant's or agent's file reference 53189Awo	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No PCT/EP2005/002036	International filing date *(day/month/year)* 23/02/2005	(Earliest) Priority Date *(day/month/year)* 24/02/2004
Applicant SCHERING AKTIENGESELLSCHAFT		

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 5 sheets

[X] It is also accompanied by a copy of each prior art document cited in the 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, unless otherwise indicated under this item

[ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23 1(b))

b [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I

2 [X] **Certain claims were found unsearchable** (See Box II)

3. [ ] **Unity of invention is lacking** (see Box III)

4 With regard to the **title**,

[ ] the text is approved as submitted by the applicant

[X] the text has been established by this Authority to read as follows

PIPERAZINE DERIVATIVES FOR THE TREATMENT OF ENDOMETRIOSIS

5. With regard to the **abstract**,

[X] 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/EP2005/002036

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

9195

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	EP 1 254 899 A (SCHERING AKTIENGESELLSCHAFT) 6 November 2002 (2002-11-06) cited in the application paragraph '0012!	1-32
X	claim 13	33
Y	WO 2004/002960 A (SCHERING AKTIENGESELLSCHAFT; DUNNING, LAURA; JAROCH, STEFAN; KOCHANNY,) 8 January 2004 (2004-01-08) page 1, line 30 - page 2, line 1; claims 20,21	1-32

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

* Special categories of cited documents

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2005	23/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Johnson, C

1

Form PCT/ISA/210 (second sheet) (January 2004)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1196

Continuation of Box II.2

Claims Nos.: 2-32 (part)

Claim 1, the main independent claim of the application, covers the use of compounds of formula (Ia) for the production of a medicament for the treatment and prevention of endometriosis, i.e. it does not claim compounds, but their specific medical uses. Claim 2 is dependent on claim 1, but refers to "the compound of claim 1". There is thus a contradiction between the claims and they do not fulfil the requirements of Article 6 PCT. It is not clear whether the subject matter to be covered by the dependent claims should be the compounds per se or their use for the production of a medicament. The description refers to 2 published patent applications by the present applicant and states that they disclose piperazine derivatives comprised in the present application, but that they do not describe their use for the treatment of endometriosis. It thus appears that the applicant is aware that the present piperazine derivatives are not new, and only intends to cover their specific use for the prevention/treatment of endometriosis. The present search and examination has thus only been based on this use, and the compounds per se have not been searched or examined.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/002036

1198

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

1197

1 [ ] Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely.

2 [X] Claims Nos 2-32 (part)
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

see FURTHER INFORMATION sheet PCT/ISA/210

3 [ ] Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2 [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos..

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest

[ ] No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/002036

1198

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 1254899	A	06-11-2002	US	6207665	B1	27-03-2001
			EP	1254899	A2	06-11-2002
			AT	232522	T	15-02-2003
			AU	735462	B2	12-07-2001
			AU	8625898	A	30-12-1998
			CA	2293382	A1	17-12-1998
			DE	69811363	D1	20-03-2003
			DE	69811363	T2	27-11-2003
			DK	988292	T3	22-04-2003
			EA	4038	B1	25-12-2003
			EE	9900565	A	15-06-2000
			EE	200200682	A	15-04-2003
			EE	200200683	A	15-04-2003
			EE	200200684	A	15-04-2003
			WO	9856771	A2	17-12-1998
			EP	0988292	A2	29-03-2000
			ES	2191320	T3	01-09-2003
			HU	0003929	A2	28-05-2001
			IL	132398	A	31-08-2004
			JP	2002503239	T	29-01-2002
			NO	996068	A	11-02-2000
			NO	20031373	A	11-02-2000
			PL	337758	A1	11-09-2000
			SK	171399	A3	12-09-2000
			TR	9903034	T2	21-06-2000
			US	2003158205	A1	21-08-2003
			US	2003139425	A1	24-07-2003
			US	6541476	B1	01-04-2003
			US	6534509	B1	18-03-2003
			US	6573266	B1	03-06-2003
			US	2002177598	A1	28-11-2002
WO 2004002960	A	08-01-2004	AU	2003247772	A1	19-01-2004
			BR	0312204	A	26-04-2005
			CA	2489560	A1	08-01-2004
			WO	2004002960	A1	08-01-2004
			US	2004072818	A1	15-04-2004

Industria y Come
SUPERINTENDEN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-095141- -00000-0000
Fec 2006-09-21 16:47:35 Dep. 2020 NUECREACIONES
Tra 11 PATENTEIYII
Eve 379 FASENACIONALII
Sal 411 PRESENTACION

1199

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) MODELO DE UTILIDAD ( )	( )	(✓)
-Indicacion de que se solicita la concesión de una patente.	( )	(✓)
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
-Descripción de la Invencion.	( )	(✓)
-Dibujos de ser estos pertinentes.	( )	(✓)
-Comprobante de Pago de las tasas establecidas.	( )	(✓)
COMPLETA (✓) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicacion de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se 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 Diseño Industrial.	( )	( )
-Datos de identificacion del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable. Fdo B

Fecha. 21- Sep- 6

1201

OLARTERAISBECK

1200

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-095141- -00000-0000
Fec 2006-09-21 16 47 35 Dep 2020 NUEVCREACIONES
Tra 11 -PATENTEIYII
Eve 379 FASENACIONALII

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 29-09-06

(1) **SOLICITUD DE:**

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SCHERING AKTIENGESELLSCHAFT
Dirección: Müllerstrasse 178, 13353, Berlin Alemania
Nacionalidad o Domicilio: ALEMANA
Lugar de Constitución: ALEMANIA
Teléfono: Fax:
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) **REPRESENTANTE APODERADO**

Nombre: J. IAN RAISBECK
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 Fax: 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.376.996 Btá
TP 135.799

(4) **INVENTOR (ES) (72)**

Nombre: RICHARD HORUK, ULRIKE KAUFMANN
Dirección: 3410 Silver Springs Court, Lafayette, California CA 94549, E.U.A. y Dorotheenstrasse 56, 10117, Berlin, Alemania;
Nacionalidad o Domicilio: ESTADOUNIDENSE, ALEMANA

(5) **PCT (86)**
Solicitud Internacional No. PCT/EP2005/002036 Fecha Febrero 23, 2005
Publicación Internacional No. WO 2005/079769 Fecha Septiembre 1, 2005

(6) **Título (54):** PIPERAZINAS DERIVADAS DE UREA PARA EL TRATAMIENTO DE LA ENDOMETROSIS

(7) **Clasificación Internacional (51)** A61K 31/00

(8) **Prioridad**
SI [X] NO [ ]

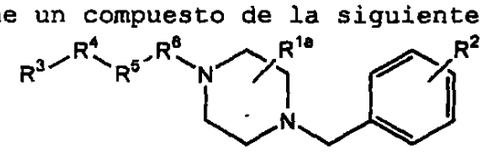
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Febrero 24, 2004	04090065.6

(9) **Comprobante de pago No.** 06 72,730 **Fecha** Septiembre 20 2006

1201

REIVINDICACIONES

1. Uso de un compuesto de la siguiente fórmula (Ia):



(Ia)

en la producción de un medicamento para el tratamiento y la prevención de la endometrosis en seres humanos en donde:

R^{1a} es

uno o más sustituyentes seleccionados entre el grupo formado por oxo, halo, (C1-C8)alquilo, (C3-C10)cicloalquilo, (C3-C10)cicloalquil(C1-C8)alquilo, (C3-C10)cicloalquilamino(C1-C8)alquilo, ((C3-C10)cicloalquil(C1-C8)alquil) amino(C1-C8)alquilo, halo(C1-C8)alquilo, (C2-C8)alquenilo, (C2-C8)alquinilo, fenilo o naftilo opcionalmente sustituido, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C2- C8)alquenilo, formilo, formil(C1-C8)alquilo, hidroxi(C1-C8)alquilo, hidroxi(C2-C8)alquenilo, hidroxi(C2-C8)alquinilo, (hidroxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (hidroxi) (C3-C10)cicloalquil(C1-C8)alquilo, mercapto(C1-C8)alquilo, ciano(C1-C8)alquilo, halo(C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-

C8)alcoxi)(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)(C1-C8)alcoxi(C1-C8)alquilo, (C1-C8)alquiltio(C1-C8) alquilo, (C1-C8)alquilsulfinil(C1-C8)alquilo, (C1-C8)alquilsulfonil(C1-C8)alquilo, hidroxi(C1-C8)alquiltio(C1-C8)alquilo, amino(C1-C8)alquilo, mono(C1-C8) alquilamino(C1-C8)alquilo, di(C1-C8)alquilamino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)amino(C1-C8)alquilo, mono(fenilo o naftilo opcionalmente sustituido)(C1-C8)alquilamino(C1-C8)alquilo, (C1-C8) alquilcarbonilamino(C1-C8)alquilo, ((C1-C8)alquilcarbonil)((C1-C8)alquil) amino(C1-C8)alquilo, azido(C1-C8)alquilo, ureido(C1-C8)alquilo, mono(C1-C8) alquilureido(C1-C8)alquilo, di(C1-C8)alquilureido(C1-C8)alquilo, ((C1-C8) alcoxicarbonil(C1-C8)alquil)ureido(C1-C8)alquilo, (C1-C8) alcoxicarbonilamino(C1-C8)alquilo, hidroxi(C1-C8)alquilamino(C1-C8)alquilo, (fenilo o naftilo opcionalmente sustituido)oxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo, (C1-C8)alcoxi(C1-C8)alquilcarboniloxi(C1-C8)alquilo,

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

1203

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
SCHERING AKTIENGESELLSCHAFT

REFERENCIA	Radicación No.	6 95141
	Solicitud internacional	PCT/EP2005/002036
	Fecha inicio fase nacional	24/09/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	013880

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior, requerimiento fue notificado por fijación en lista de fecha 01 DIC 2006
aalvarado